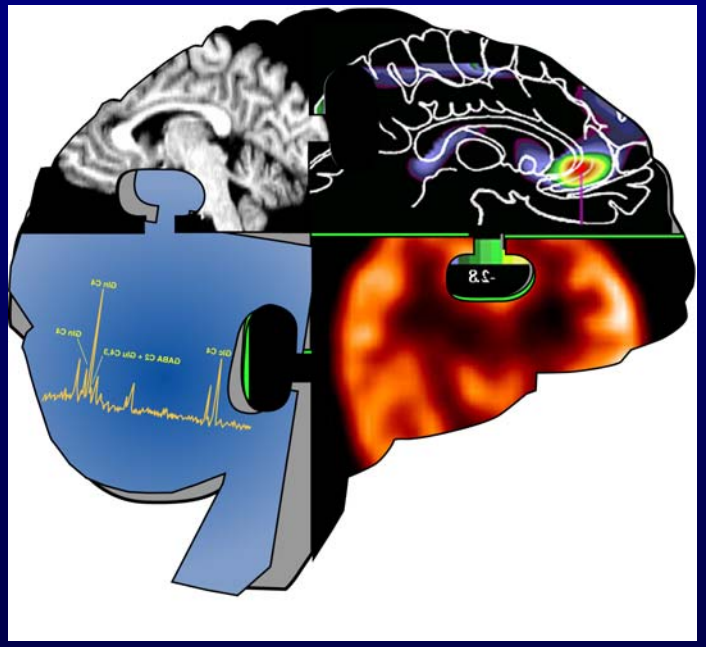
Positron Emission Tomography: Tool to Facilitate Drug Development and to Study Pharmacokinetics



October 18, 2007

Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Institute Mental Health

Outline of Talk

* PET has high sensitivity and specificity
* PET used in therapeutic drug development
* Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
* Study drug distribution: “peripheral” benzodiazepine receptor
* Study drug metabolism: inhibit defluorination

Imaging of neuroreceptors by PET

Isotope production
[^{11}C ^{18}F ^{13}N ^{15}O]

Cyclotron

$^{11}CO_2$

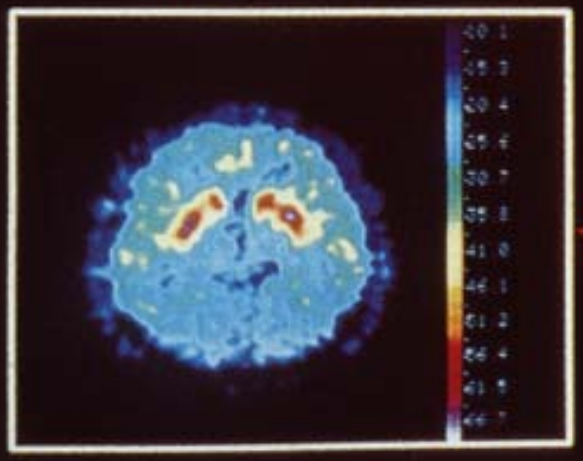
Radio chemistry

Precursor

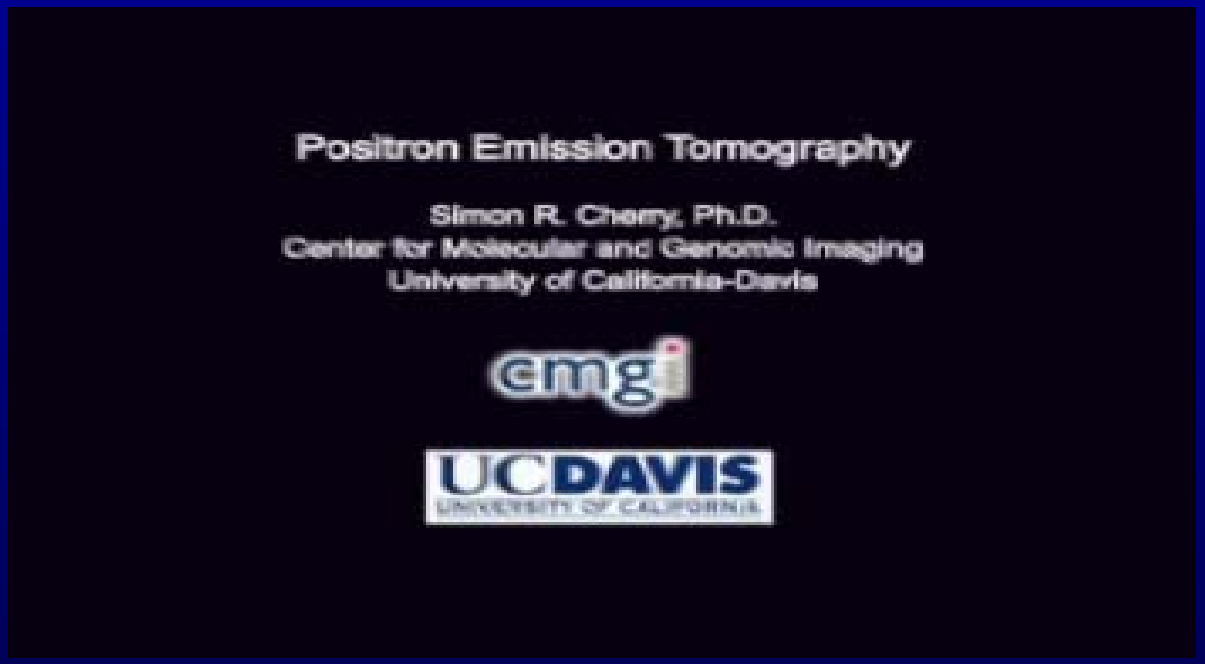
^{11}C-ligand

Positron camera

Image of
ligand distribution
in brain



Positron Emission Tomography



PET vs. MRI

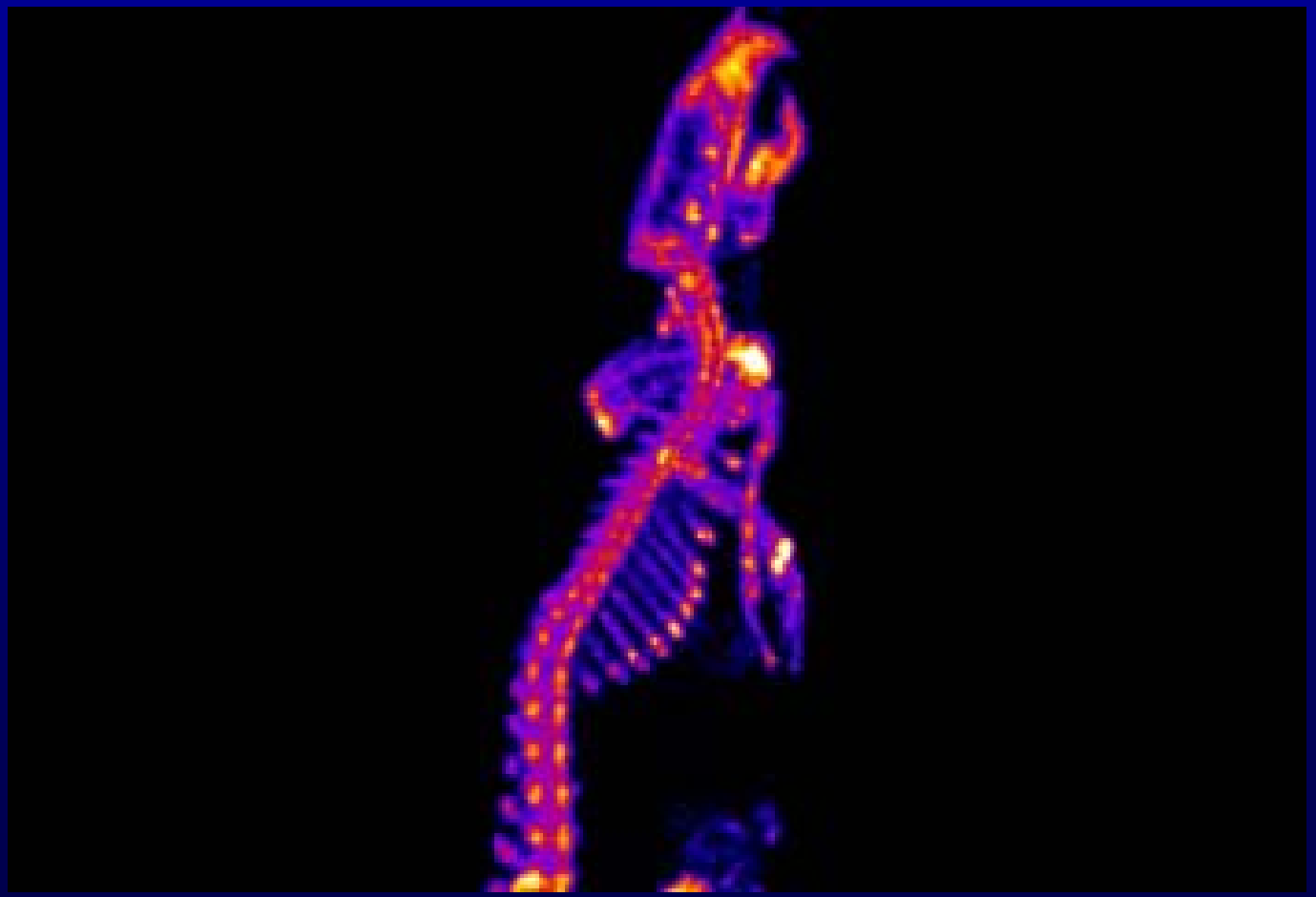
	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

Radionuclide (^{11}C): high sensitivity
Ligand (raclopride): high selectivity
Radioligand [^{11}C]raclopride: high sensitivity & selectivity

Radioligand = Drug + Radioactivity

* **Drug administered at tracer doses**
  - No pharm effects
  - Labels <1% receptors
  - Labeled subset reflects entire population
* **Radioligand disposed like all drugs**
  - Metabolism & distribution
* **Radiation exposure**

NIH Rodent PET Camera
^{18}F bone uptake rat



Developed By: Mike Green & Jurgen Seidel

PET: Tool in Therapeutic Drug Development

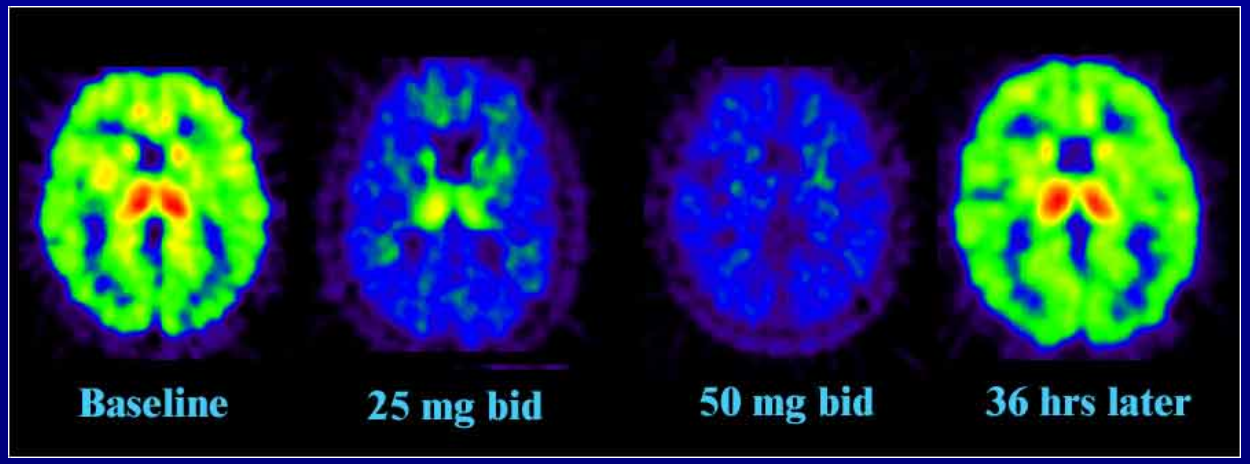
* Determine dose and dosing interval

- Identify homogeneous group

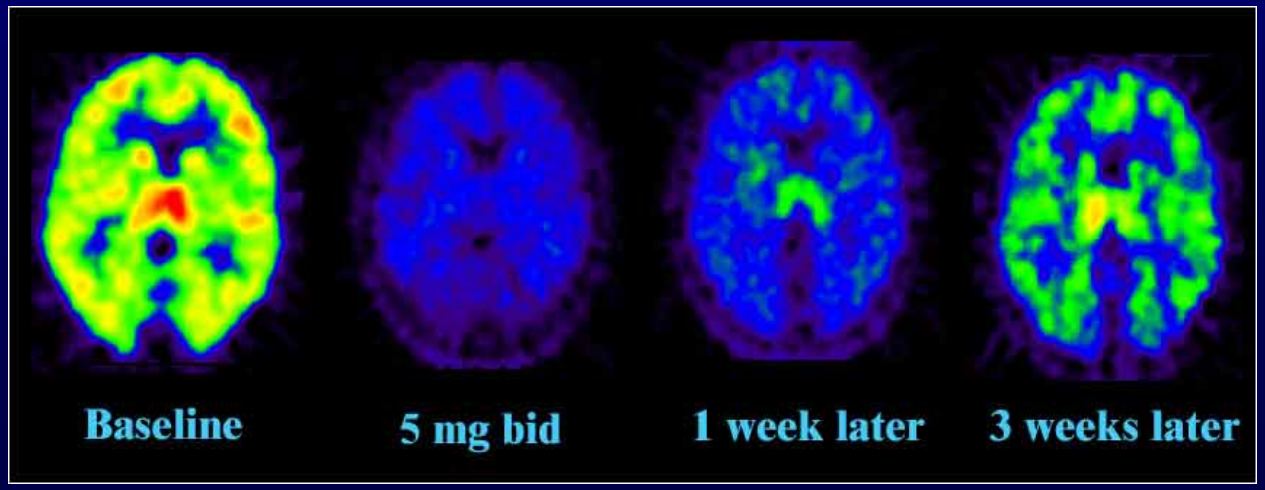
- Biomarker for drug efficacy

- Monitor gene or stem cell therapy

Lazabemide blocks [^{11}C]deprenyl binding to monoamine-oxidase-B (MAO-B)



Selegilene is more potent and longer acting than lazabemide



PET: Tool in Therapeutic Drug Development

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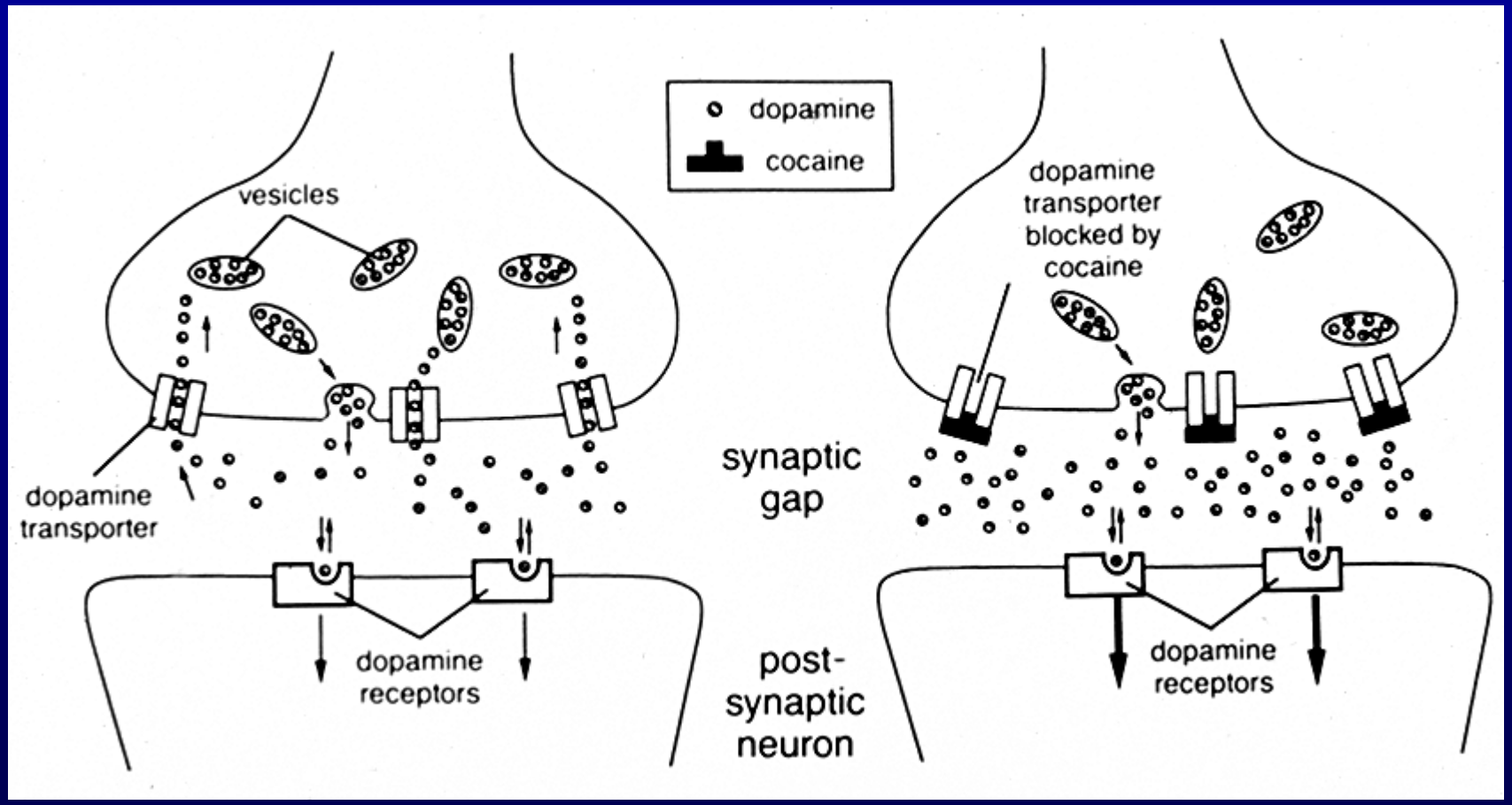
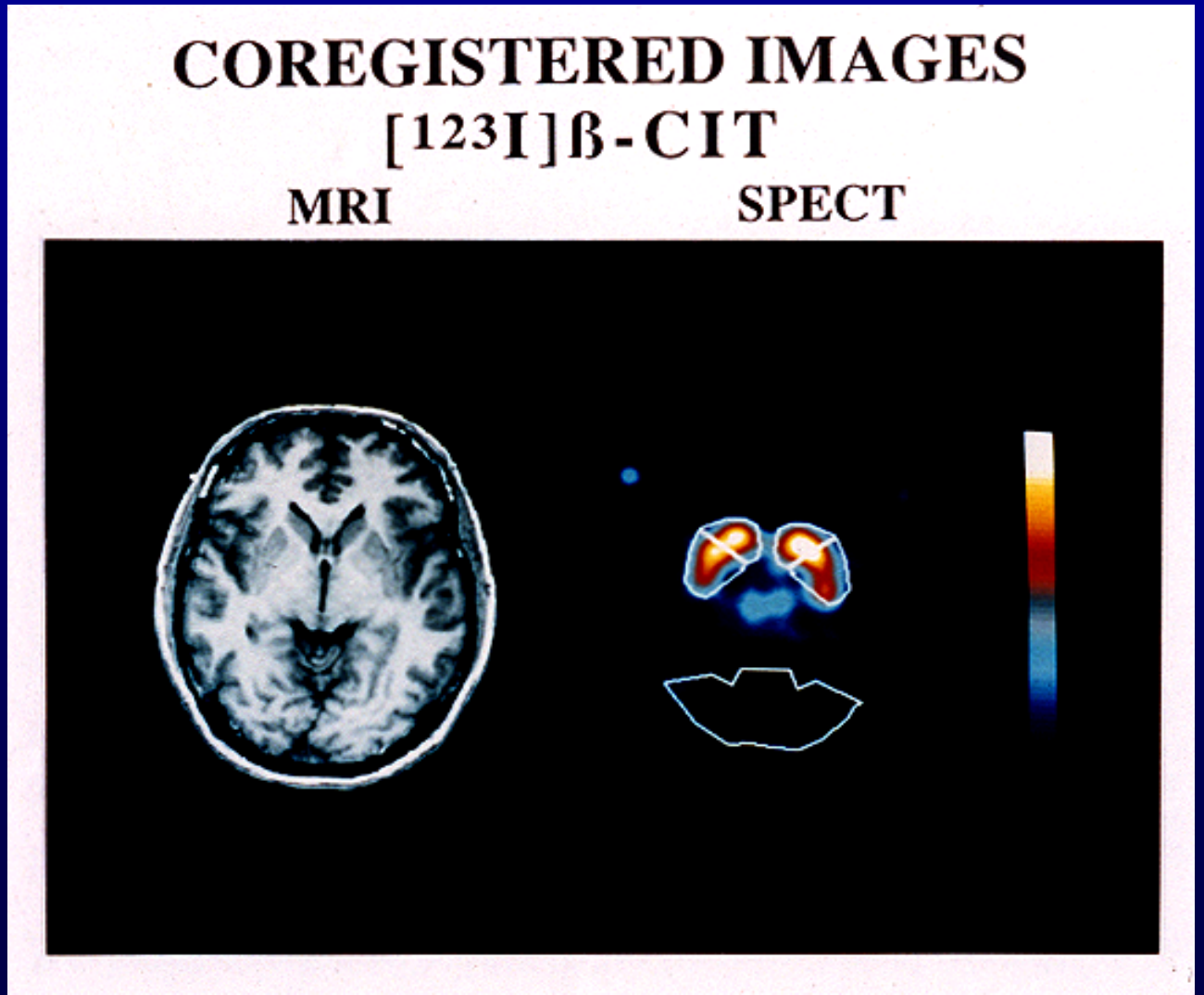
Dopamine Transporter: Located on DA Terminals Removes DA from Synapse



SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain



^{123}I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease

Healthy

Parkinson
Stage 1

PET: Tool in Therapeutic Drug Development

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- Identify homogeneous group

* Biomarker for drug efficacy

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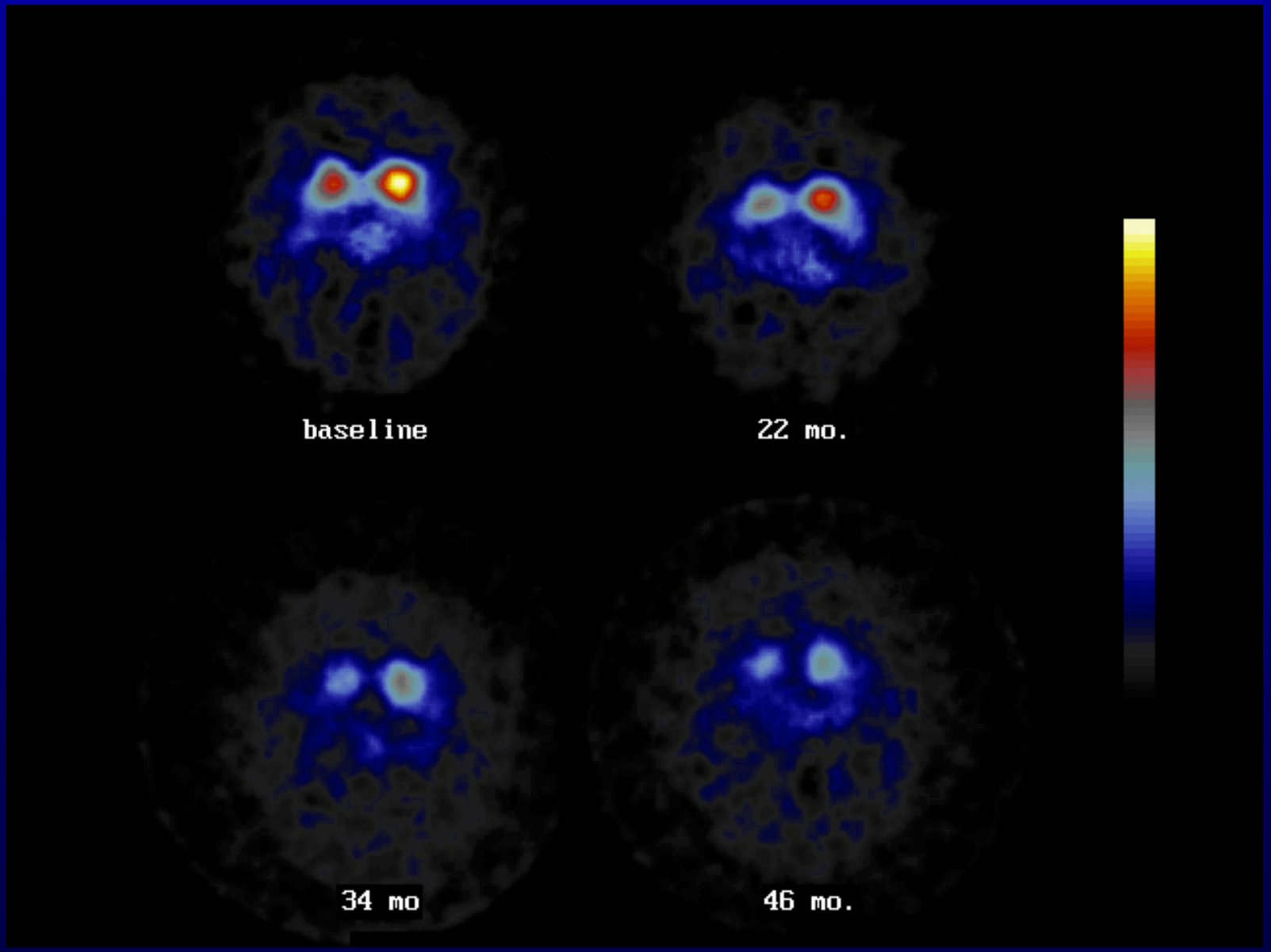
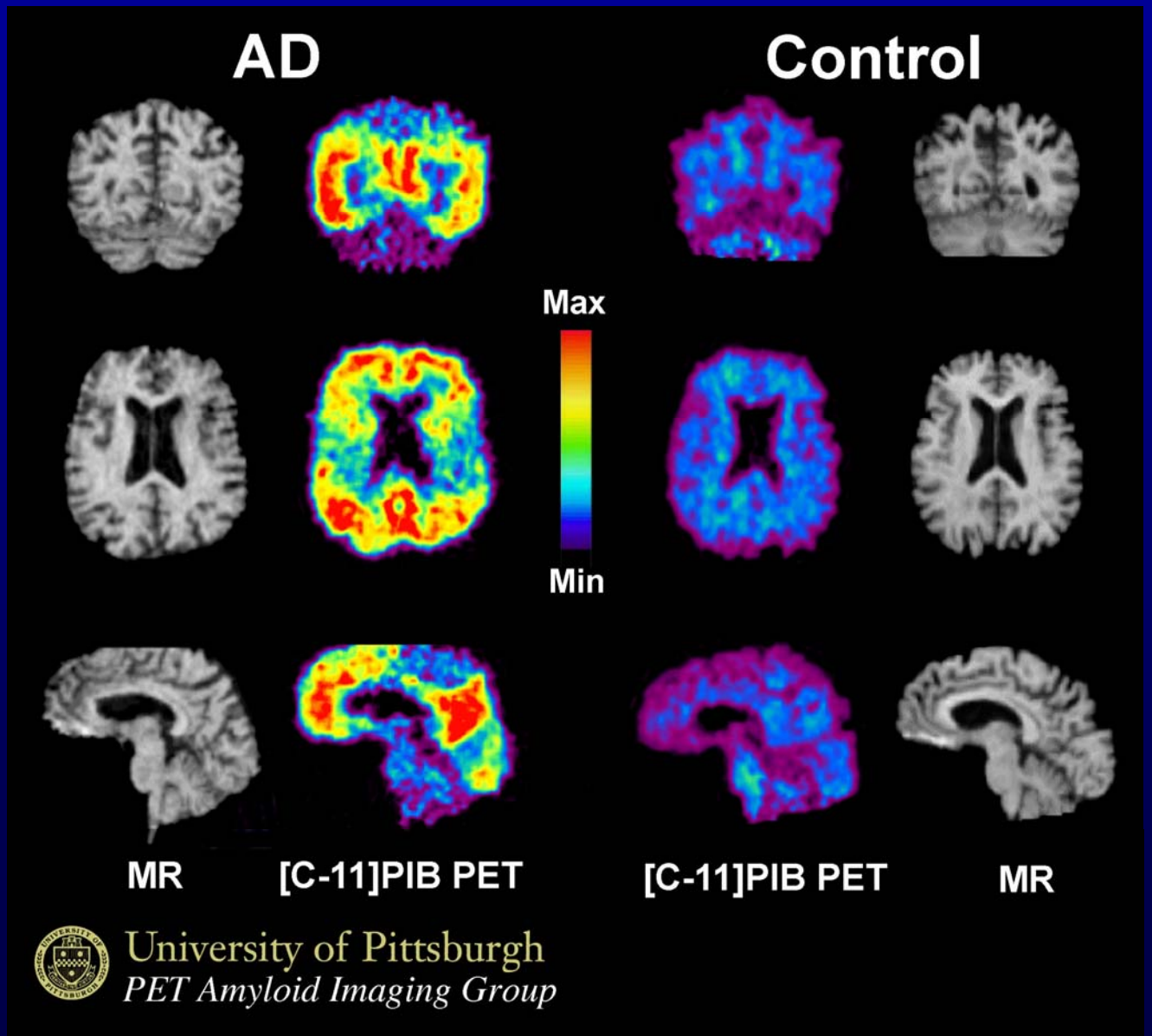
Serial Dopamine Transporter Imaging in a Parkinson Patient



PET Imaging of Amyloid: Biomarker for Alzheimer's Disease



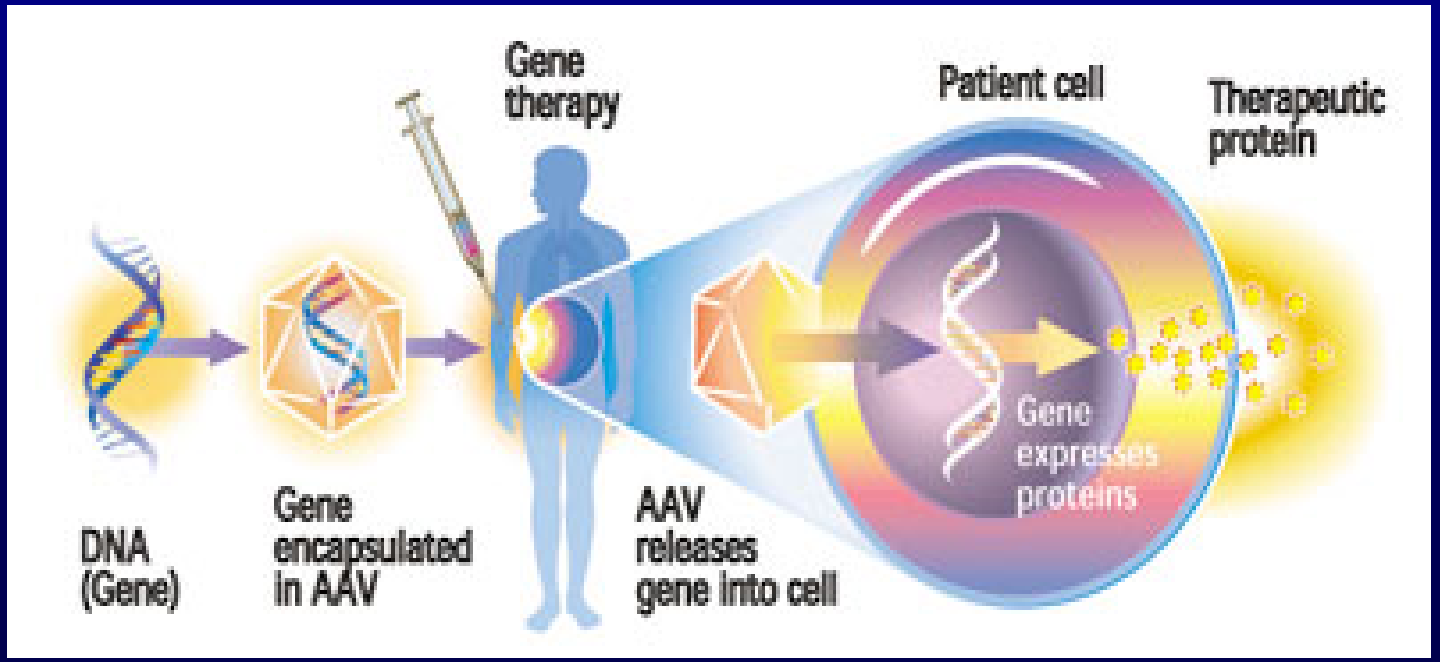
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy

* Monitor gene or stem cell therapy

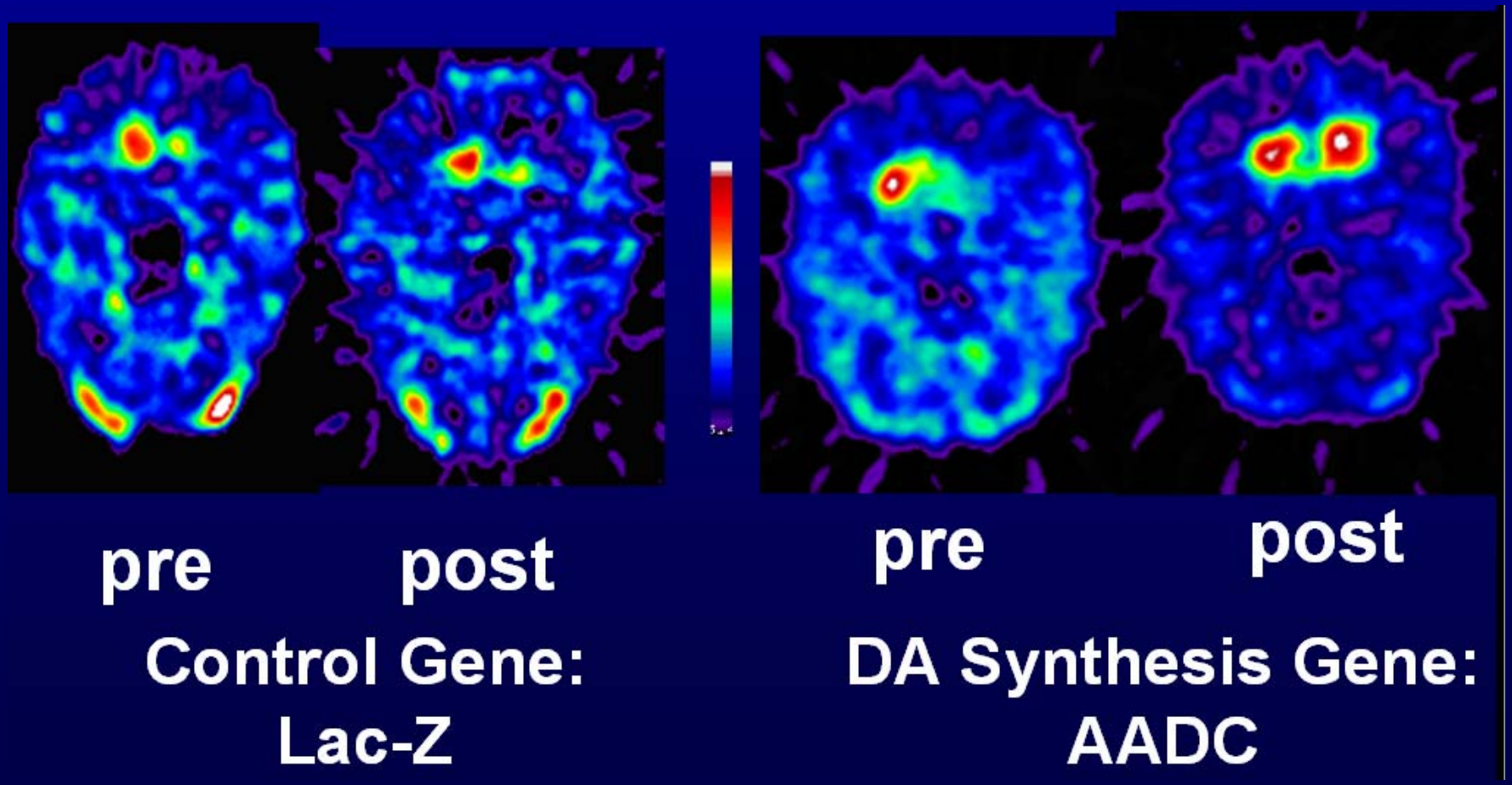
Gene Therapy Using Viral Vectors

* Viral vectors deliver gene that synthesizes dopamine (DA)
* Infuse virus into striatum (target cells)
* Target cells express the DA gene



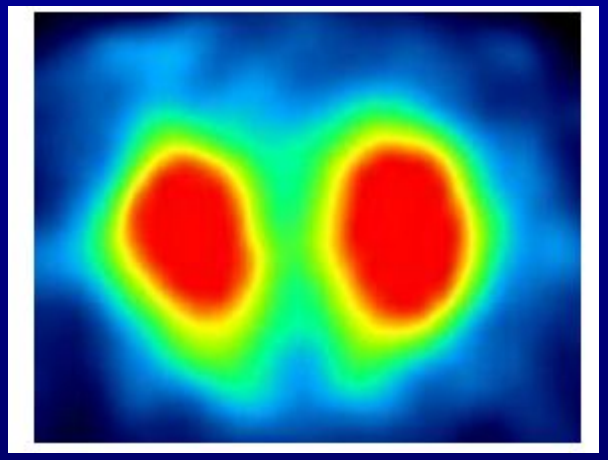
PET Dopamine Imaging in Hemi-Parkinson Monkey:

Monitors gene for DA synthesis in right striatum

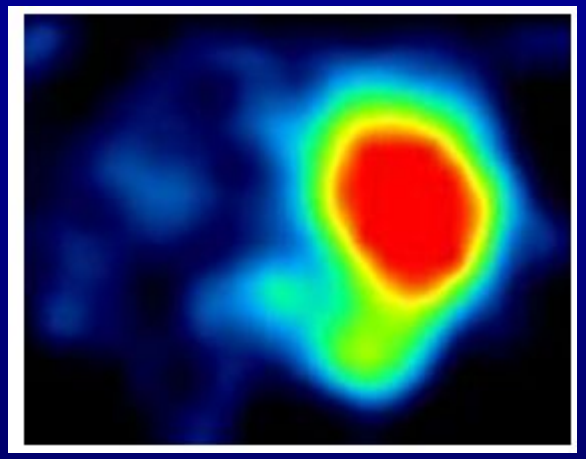


PET Imaging to Monitor Embryonic Stem Cell Treatment of "Parkinson Disease" in Rats

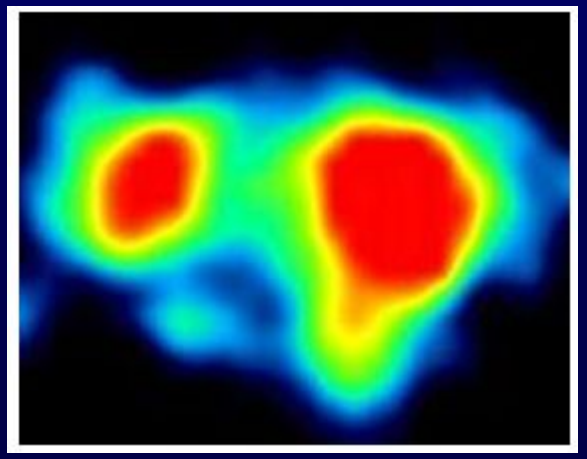
Normal



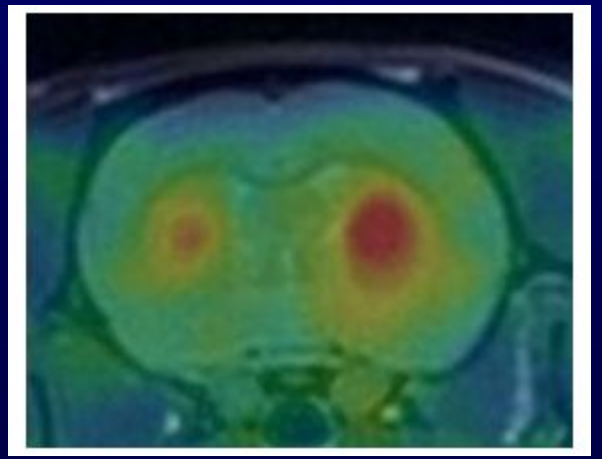
Unilateral Lesion



Embryonic Stem Cells



PET & MRI



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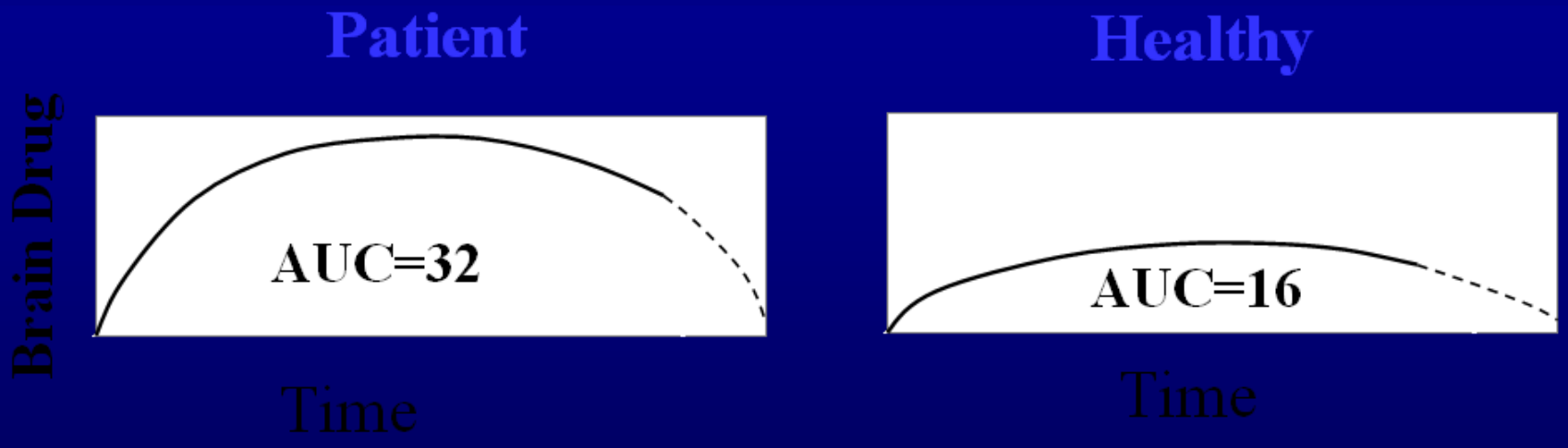
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



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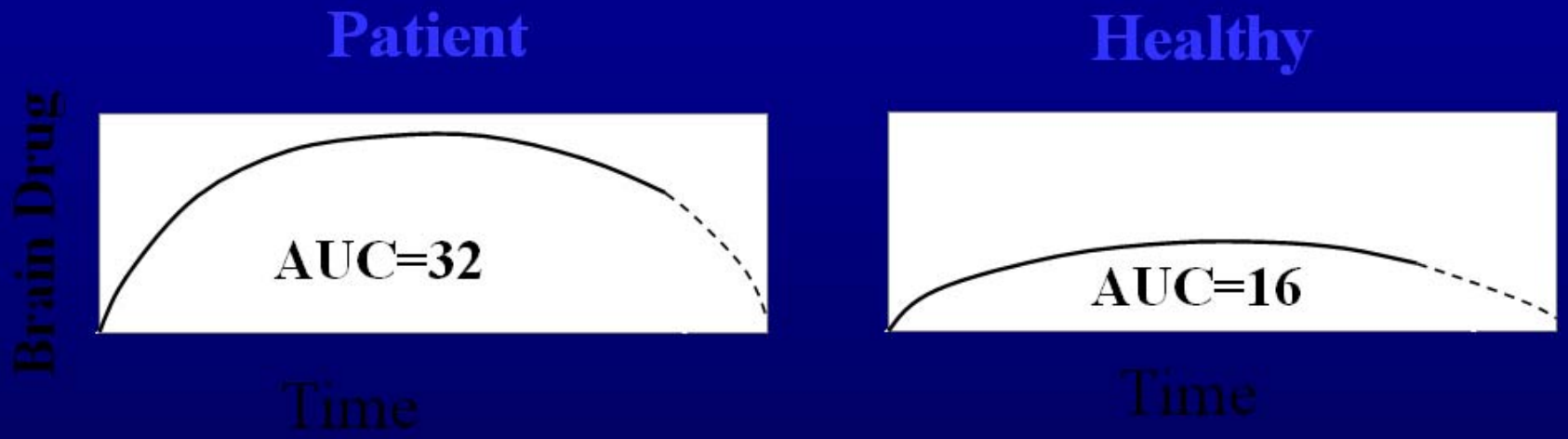
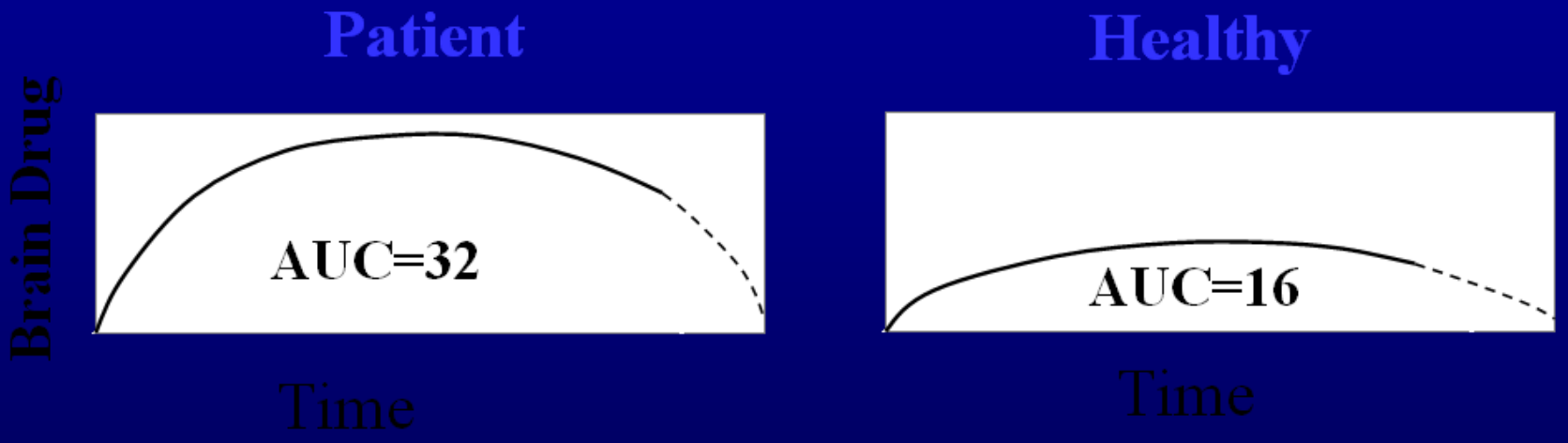


	Patient	Healthy
Inject Activity	20 mCi	10 mCi

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



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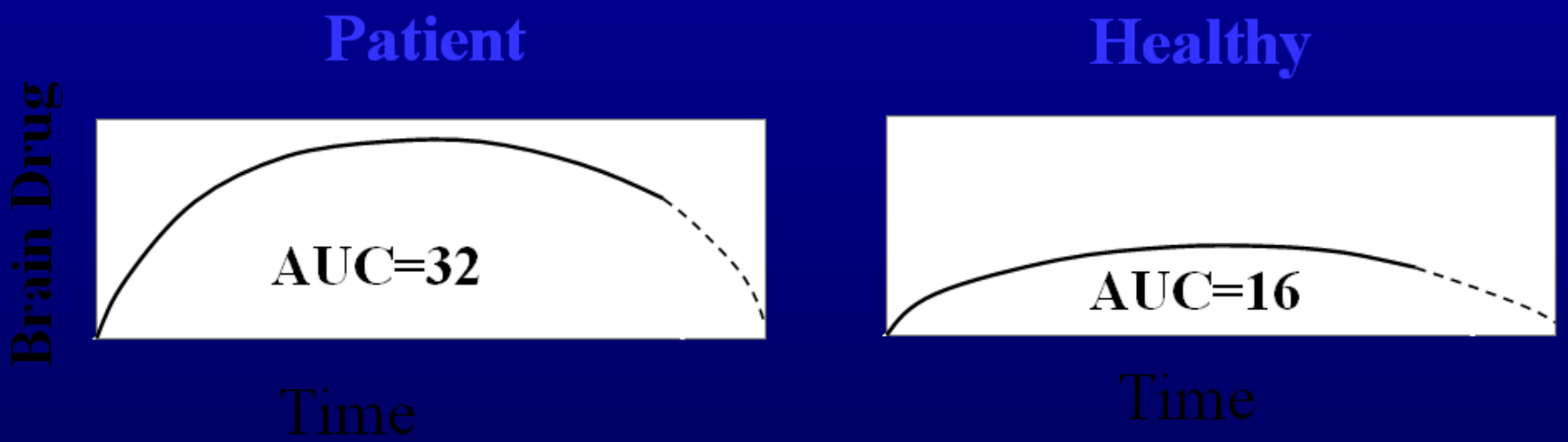
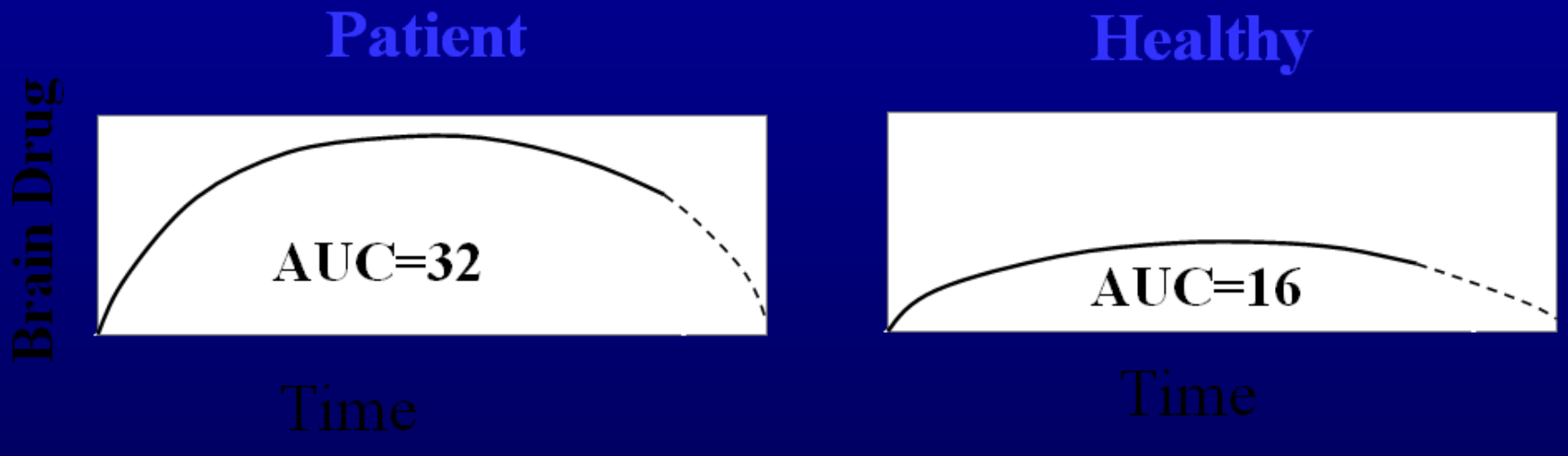


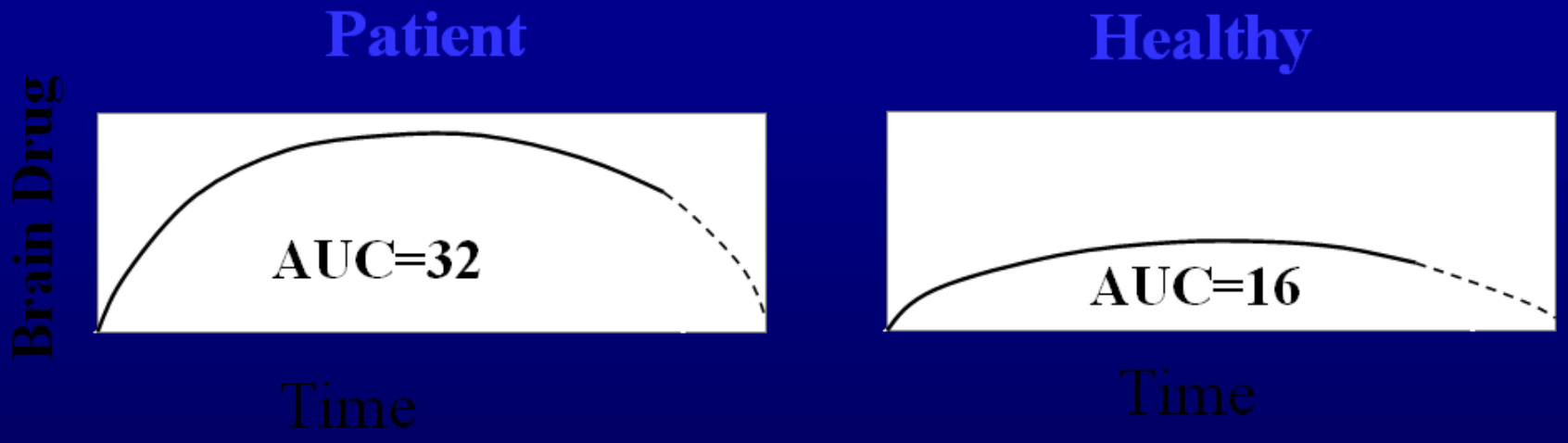
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	50 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



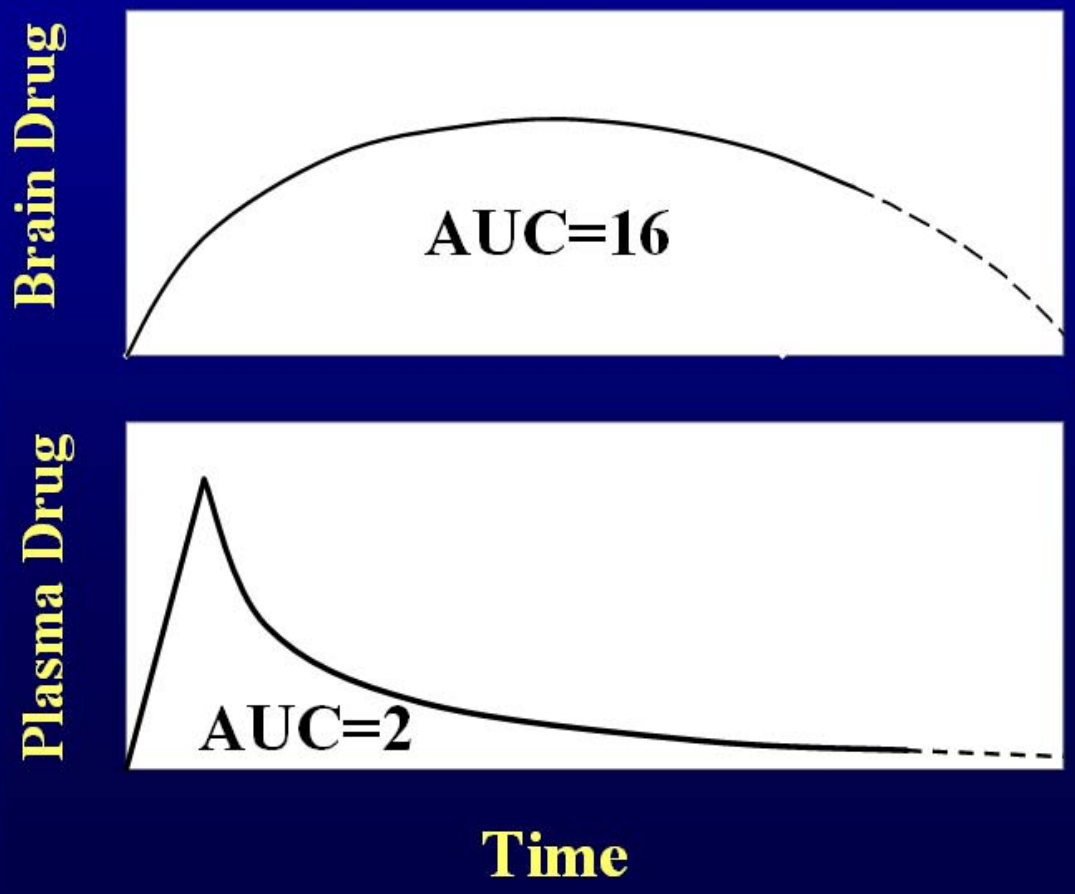
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters



	Patient	Healthy
Inject Activity	40 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No

Binding Potential (BP) BP equals uptake in brain relative to how much activity is delivered in arterial plasma



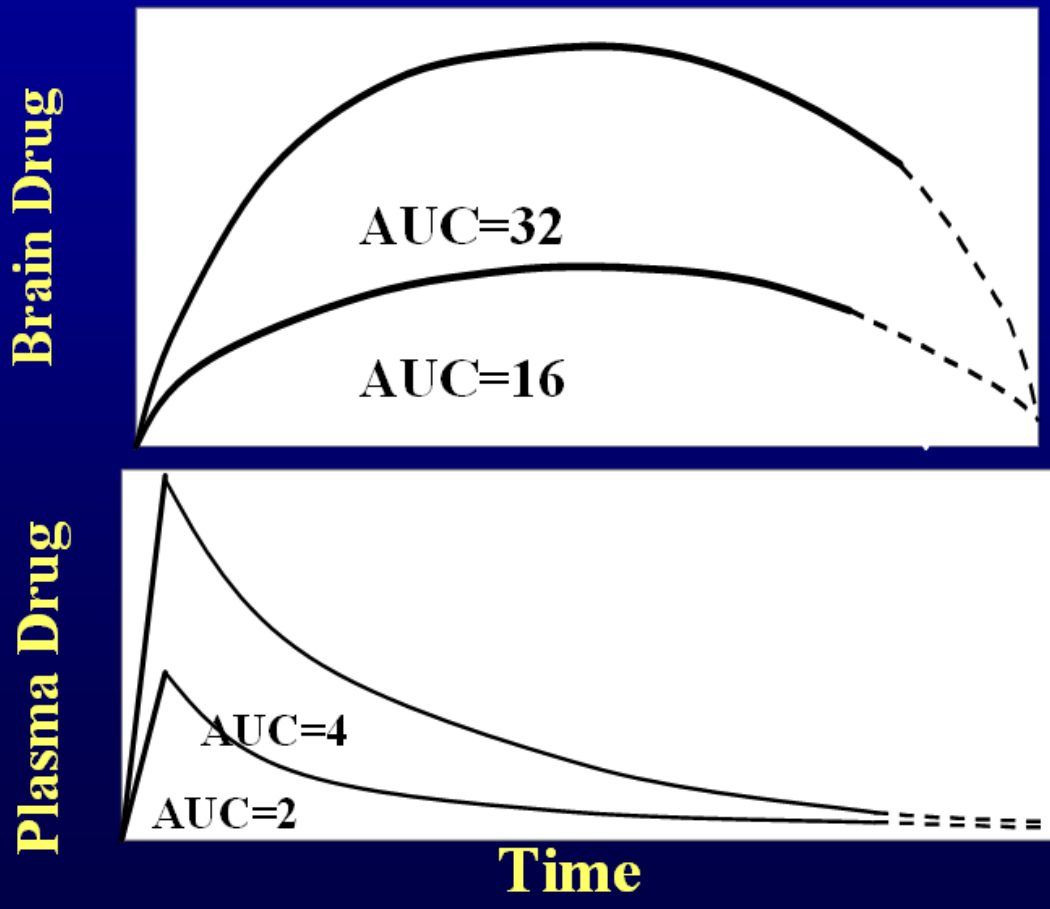
$$BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$BP = \frac{16}{2} = 8$$

Binding Potential: Independent of Injected Dose*

Double Plasma Input =>Double Brain Response

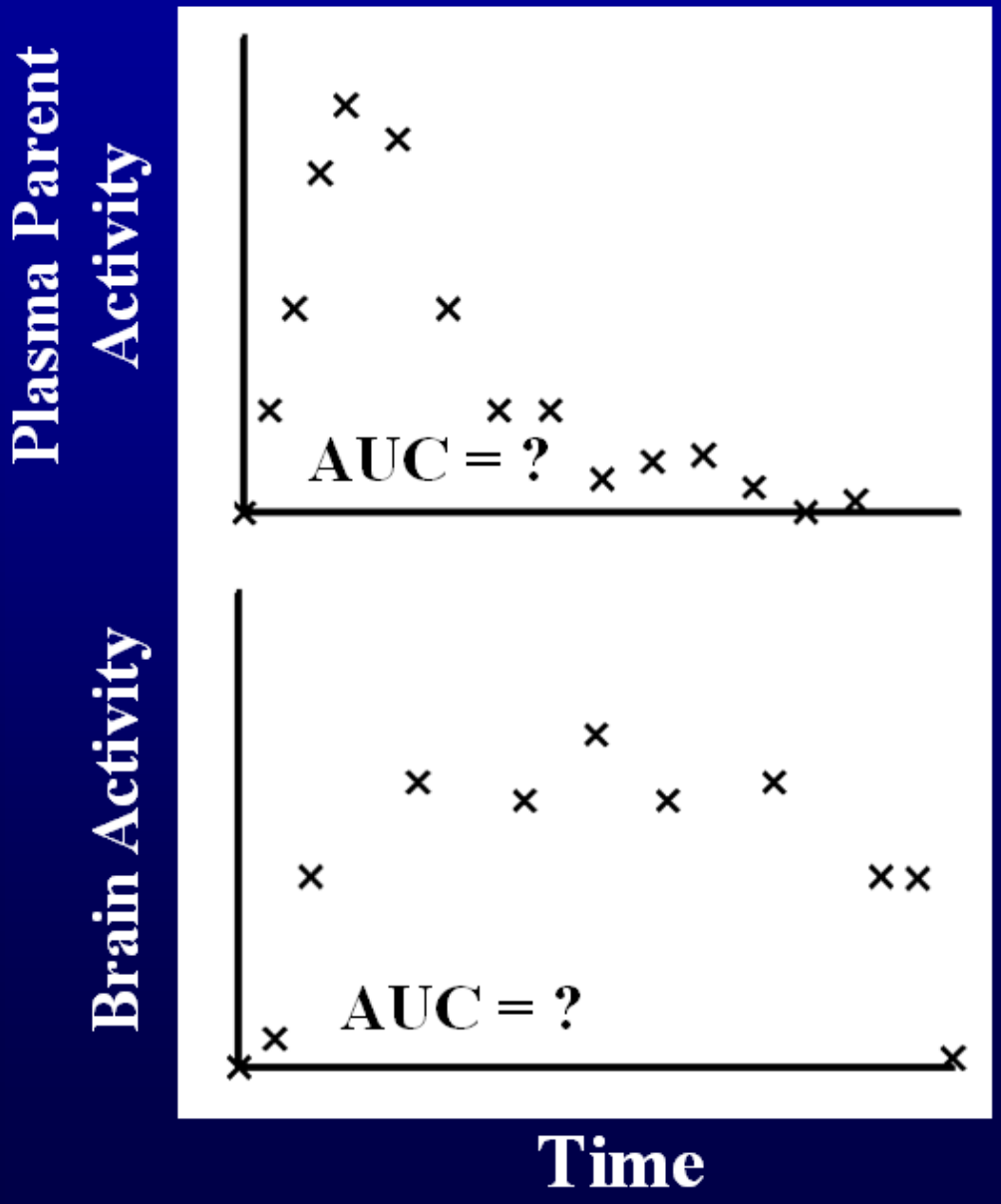
If ligand does not saturate receptors - i.e. if tracer doses used



$$\text{BP 1st Time} = \frac{32}{4} = 8$$

$$\text{BP 2nd Time} = \frac{16}{2} = 8$$

What's So difficult? Limited, noisy data.



Tissue uptake is proportional to density of receptors and the affinity of the drug

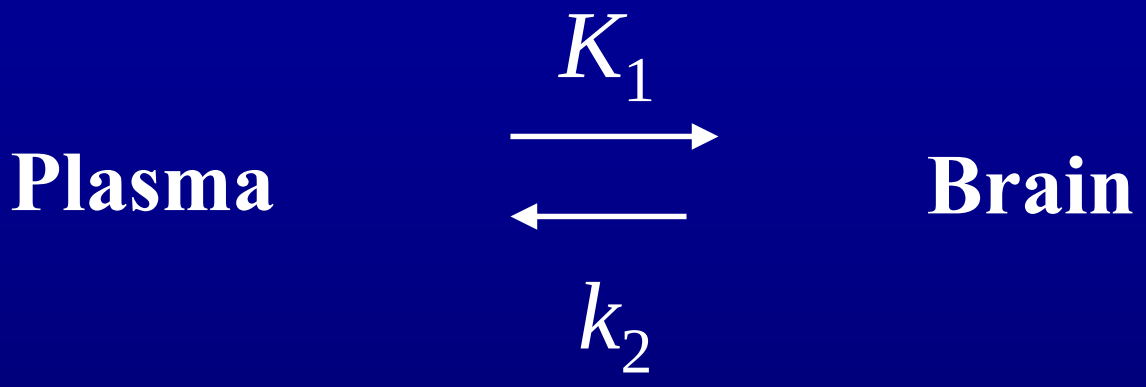
Binding Potential

$$BP = \frac{B_{max}}{K_D} = B_{max} \times \frac{1}{K_D} = B_{max} \times \text{affinity}$$

B_{max} = receptor density

K_D = dissociation binding constant

$\frac{1}{K_D}$ = binding affinity drug


K_1
Plasma
Brain
k_2

Outline of Talk

- PET has high sensitivity and specificity
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* Study drug distribution: “peripheral” benzodiazepine receptor

- Study drug metabolism: inhibit defluorination

"Peripheral" Benzodiazepine Receptor

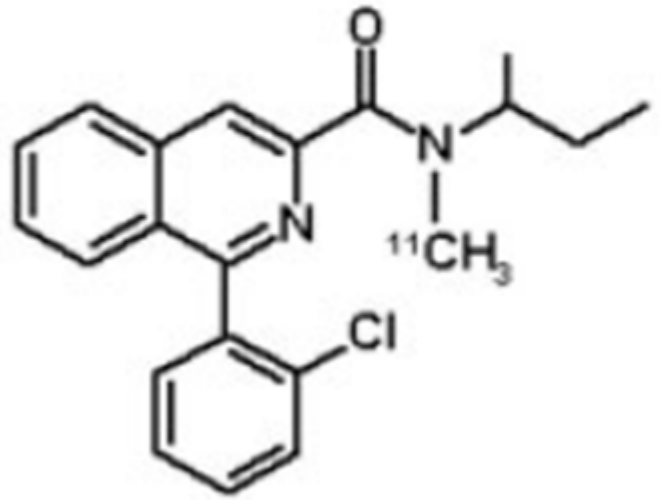
- Mitochondrial protein highly expressed in macrophages and activated microglia
- Exists in periphery and brain
- Multiple potential functions: steroid synthesis, nucleotide transport
- Distinct from typical benzodiazepine $GABA_A$ receptor in brain

* Marker for cellular inflammation

Old and New PBR PET Ligands

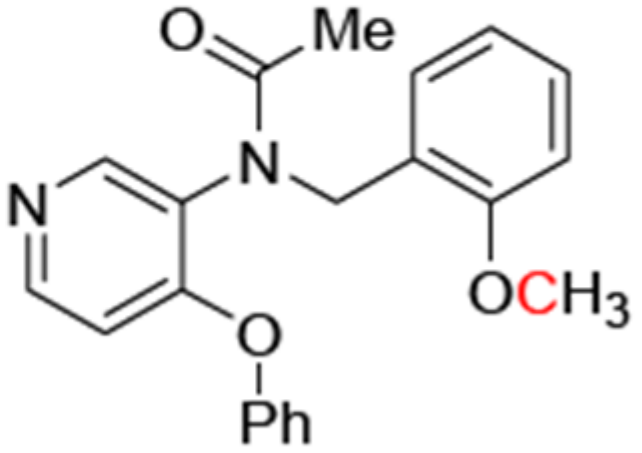
[^{11}C](*R*)-PK11195

IC50 = 0.8 nM* ; cLogP = 5.3



[^{11}C]PBR28

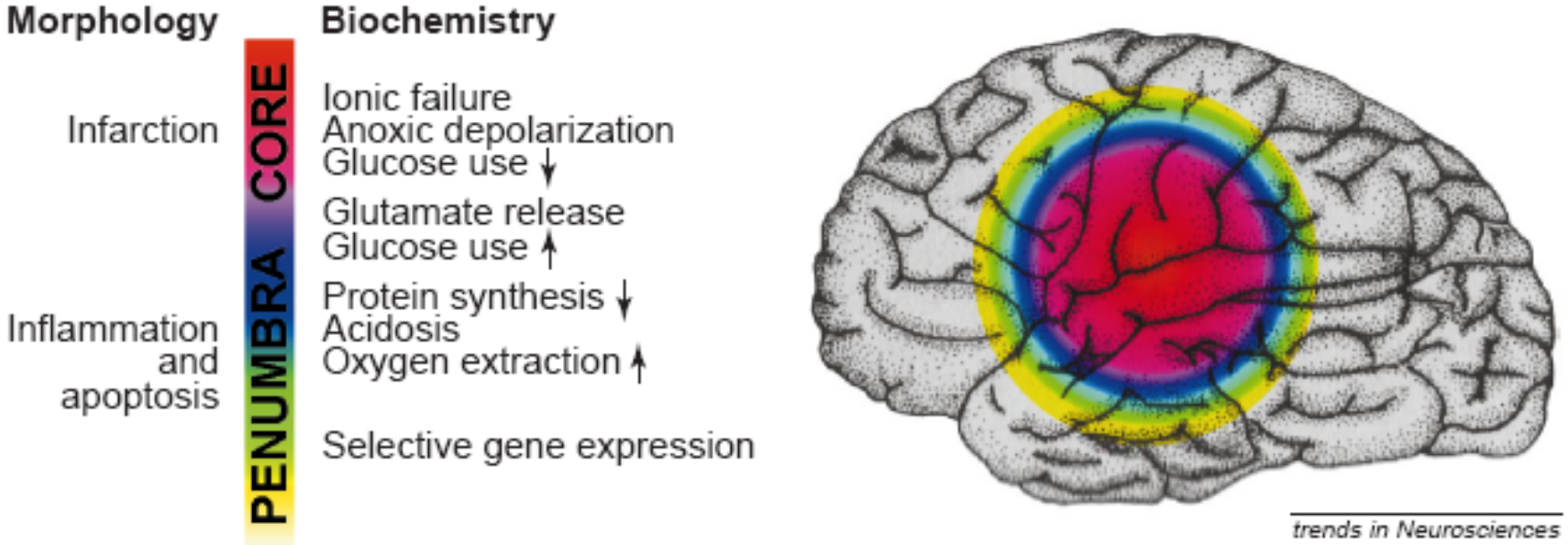
IC50 = 0.6 nM* ; cLogP = 3.0



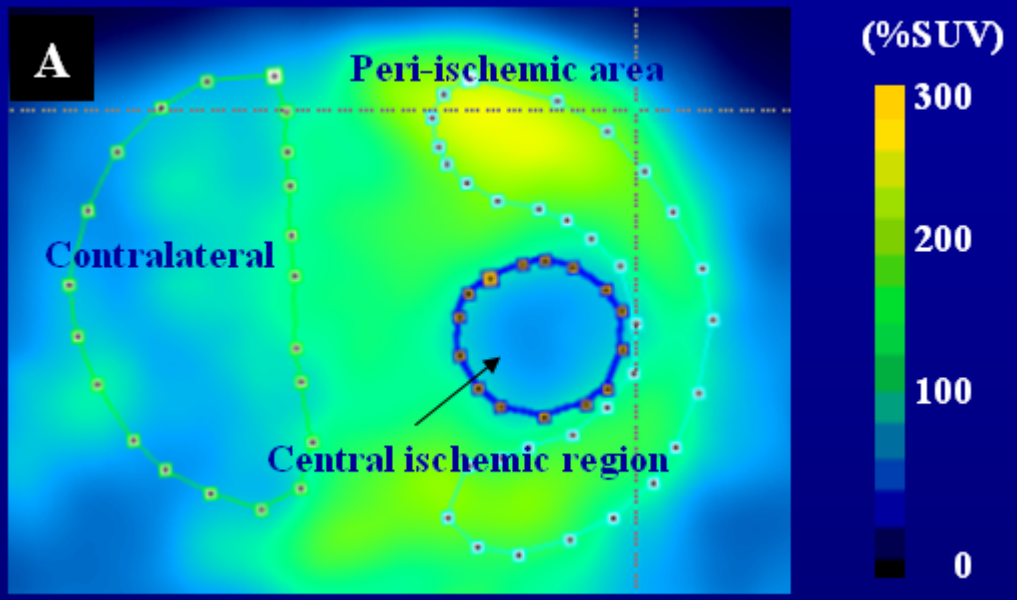
New Ligand
Aryloxyanilide Structure
Higher specific receptor signal
Lower lipophilicity

PBR Imaging in Cerebral Ischemia

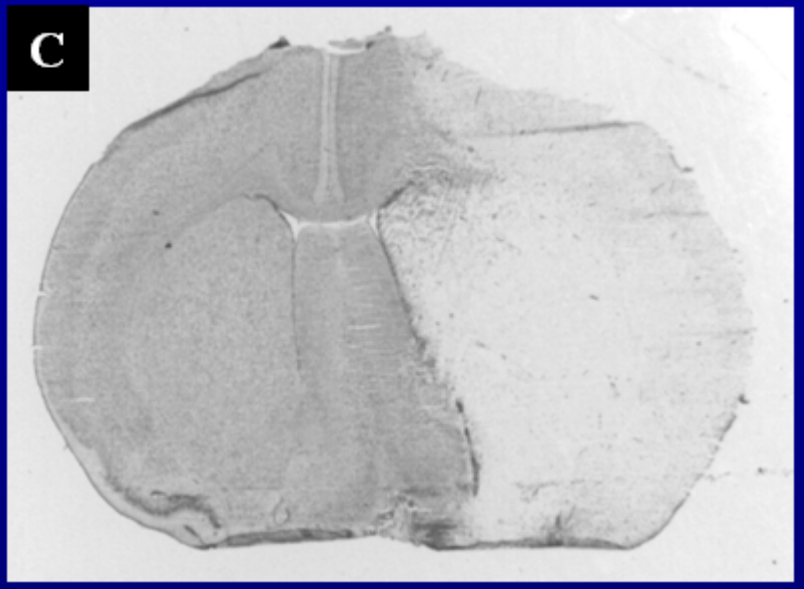
* Cerebral ischemia (stroke) consists of a necrotic core surrounded by a penumbra with salvageable tissue.
* Penumbra accumulates a large number of activated microglia.



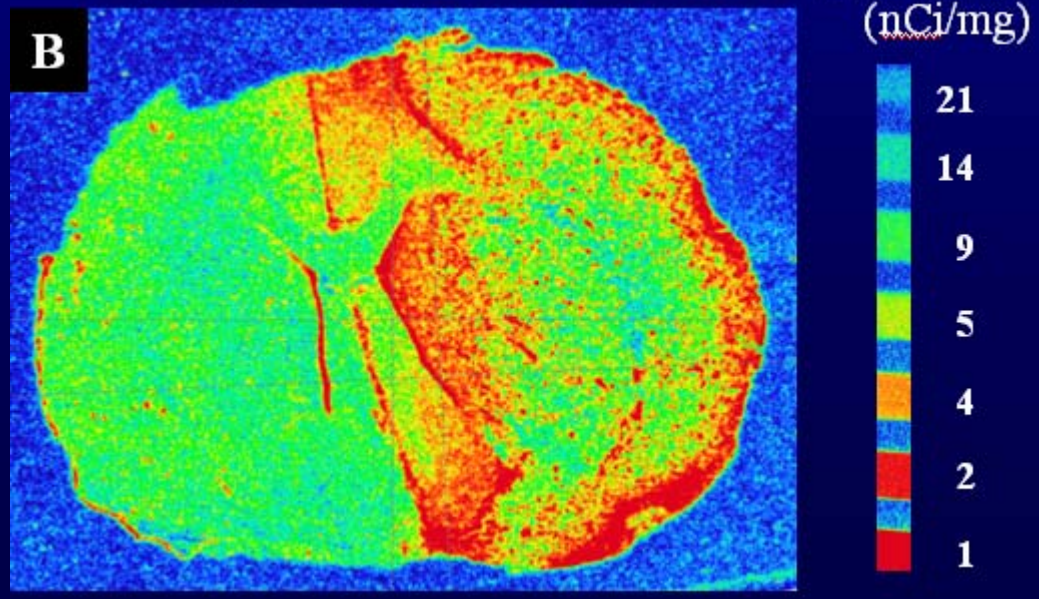
[^{11}C]PBR28 PET summation image



Cresyl violet staining

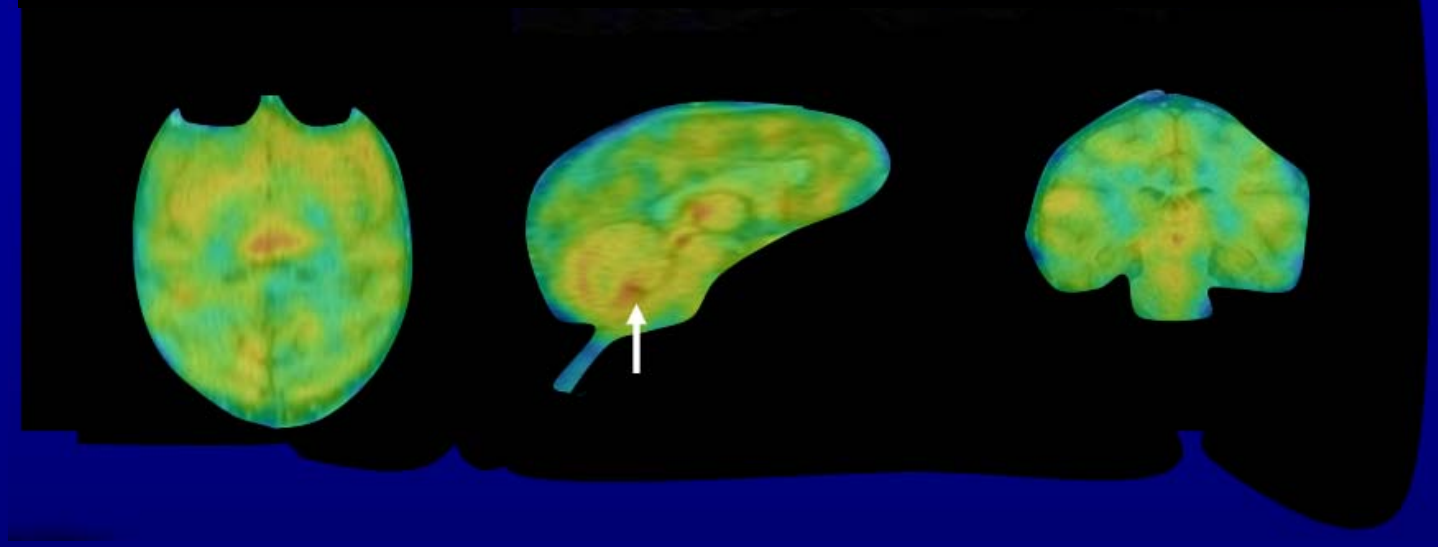


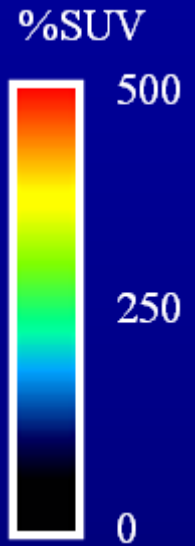
In vitro [^{3}H]PK11195 autoradiography



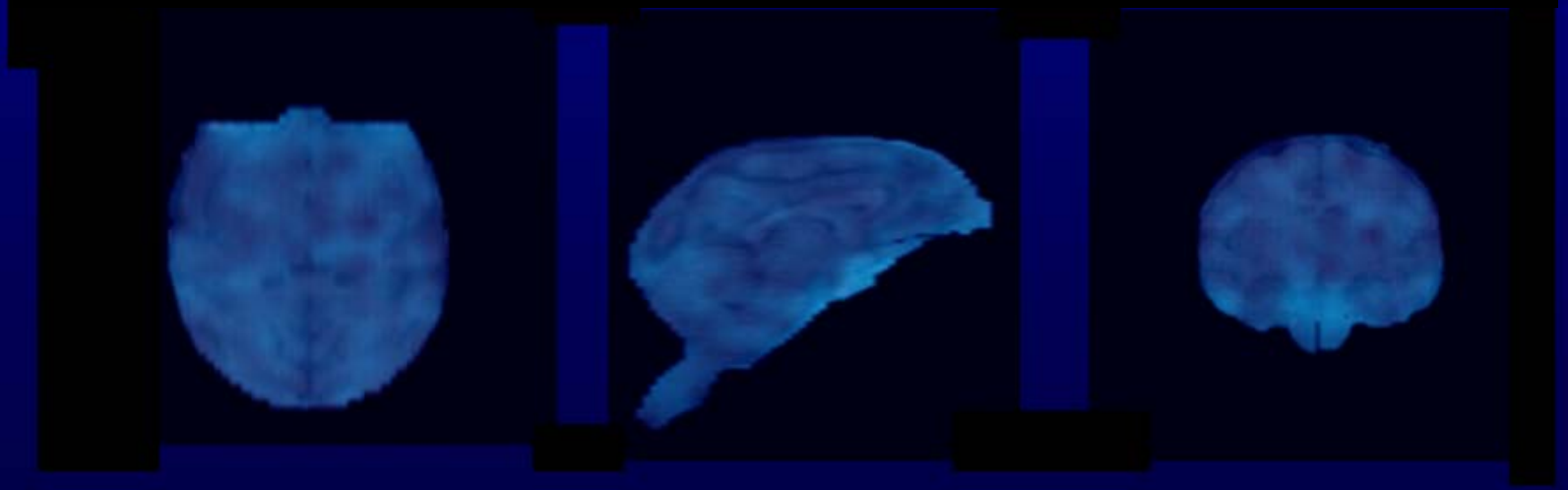
Radioactivity accumulates in the peri-ischemic area and correlates with PBR receptor autoradiography.

[^{11}C]PBR28 Monkey Brain: Total Uptake



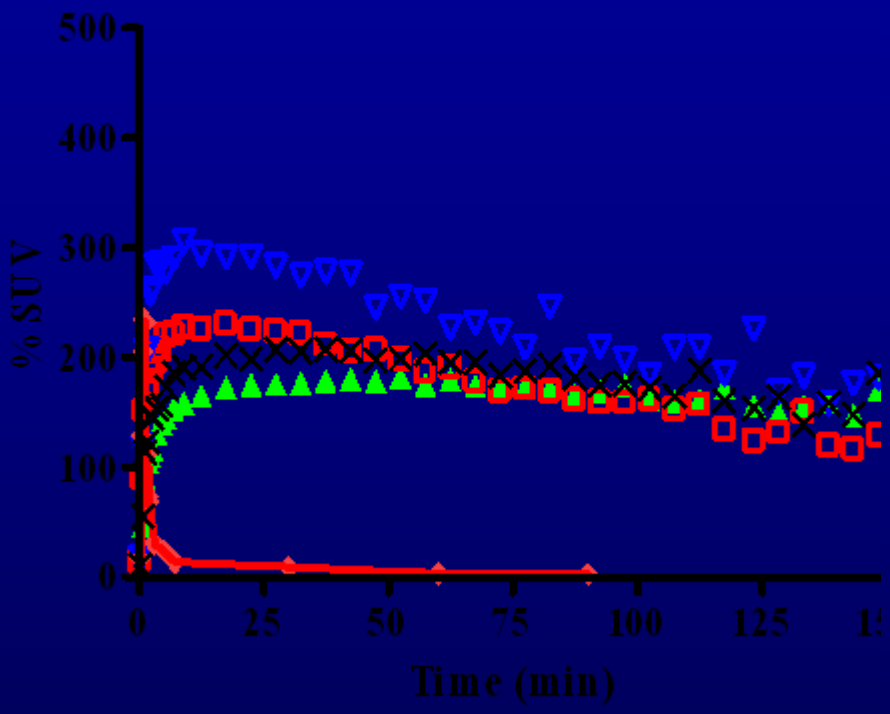


Nonspecific Uptake: Preblocked with PK11195

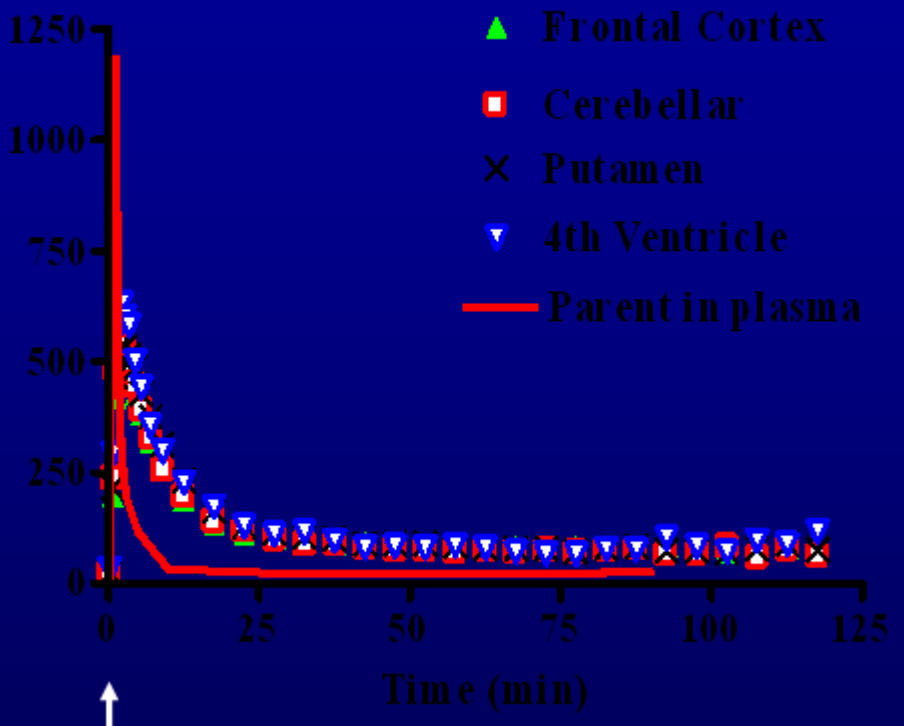


[^{11}C]PBR01 Time-activity Curves

Baseline scan



Blocking scan



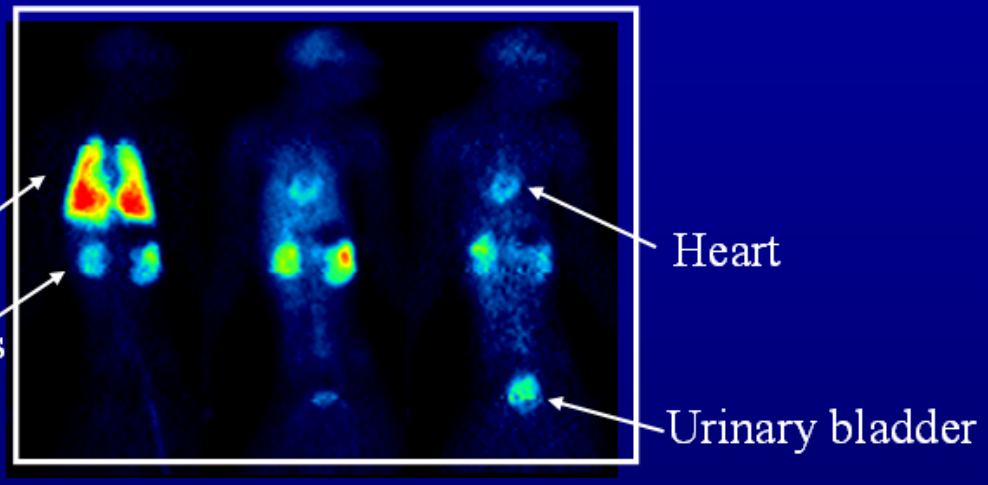
Non-radiolabeled PBR01
1 mg/kg i.v.

% standard uptake value (%SUV)
100 %SUV = Average of activity in the whole body

High levels of specific binding

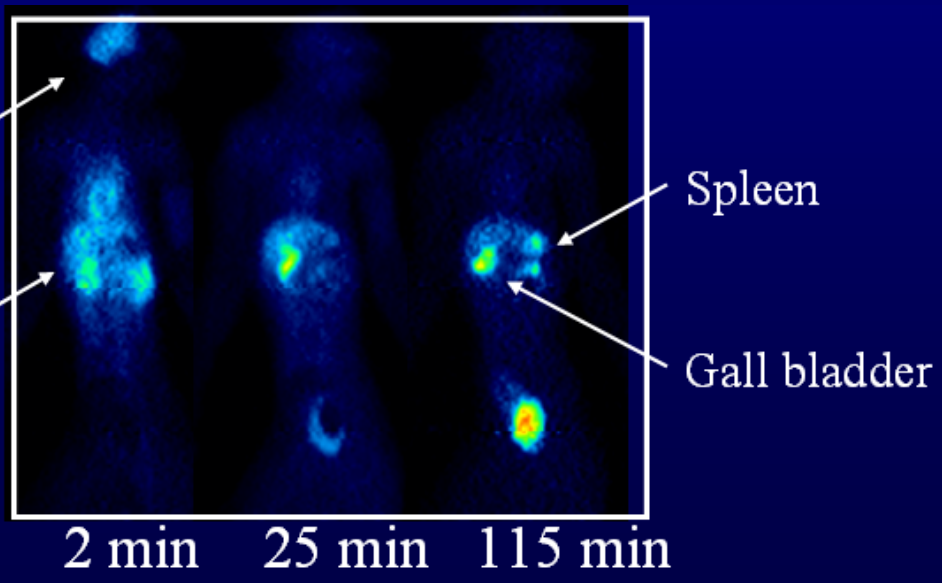
Receptor Blockade Displaces from Lung & Kidney Drives More Radioligand to Brain

Baseline

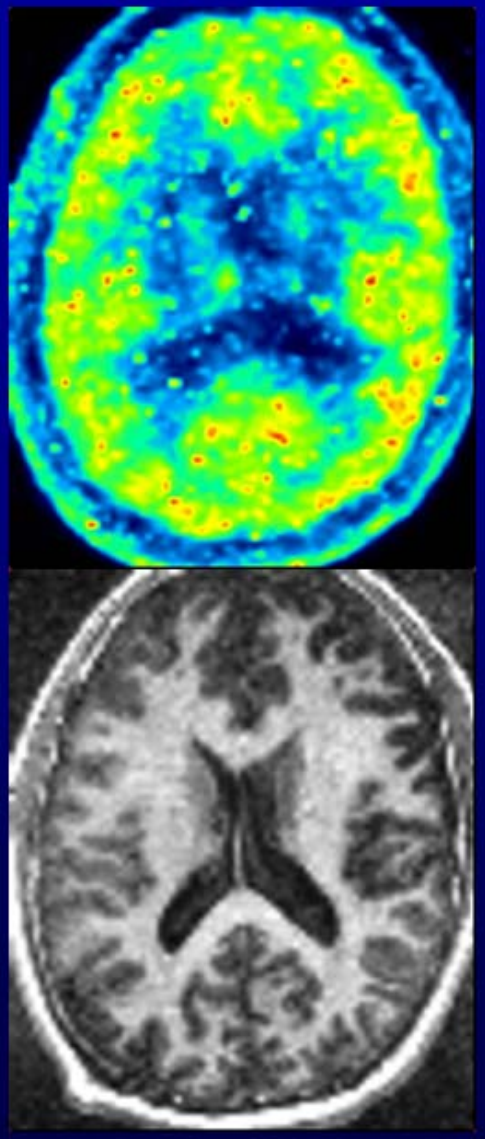


Blocked

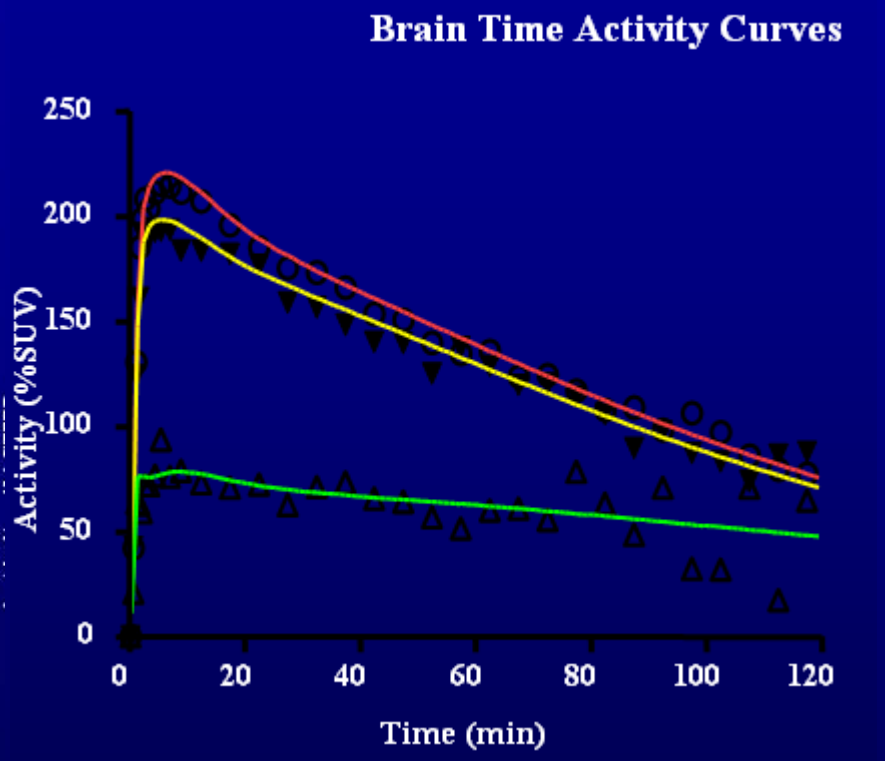
PK11195 10 mg/kg



Imaging Peripheral Type Benzodiazepine Receptors Using [^{11}C]PBR28 in Human



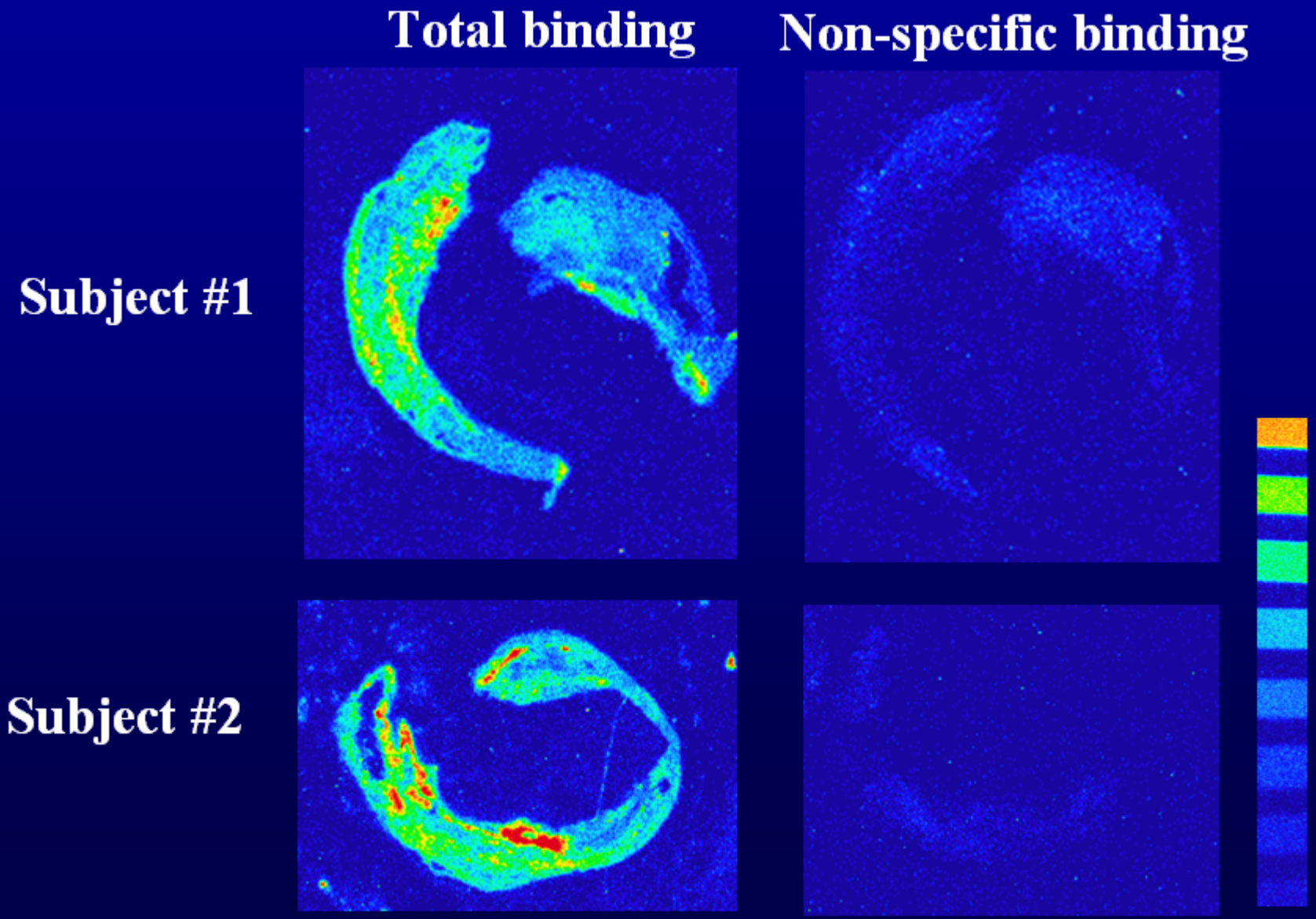
PET average all frames



Front. ctx
Thalamus
White matter

Lines are unconstrained 2-compartment fits

[^{3}H]PK 11195 Receptor Autoradiography: Human Carotid Artery with Plaque



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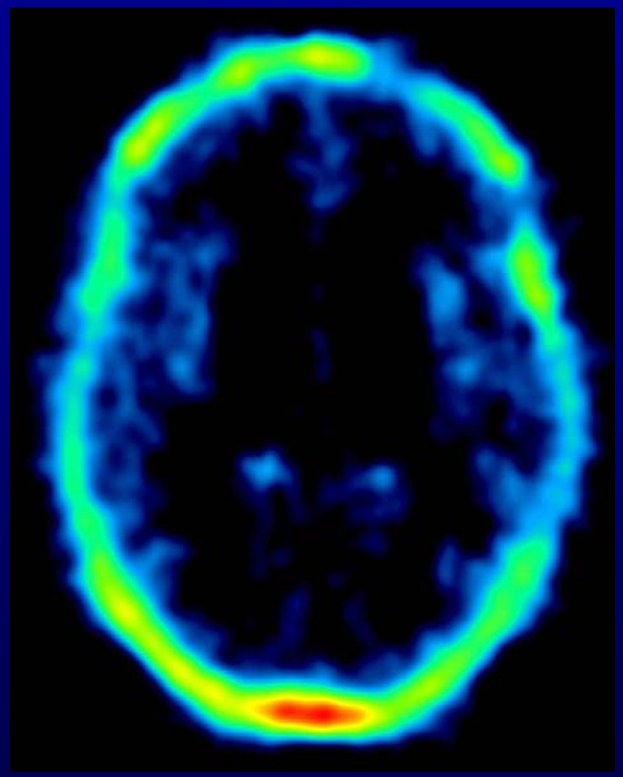
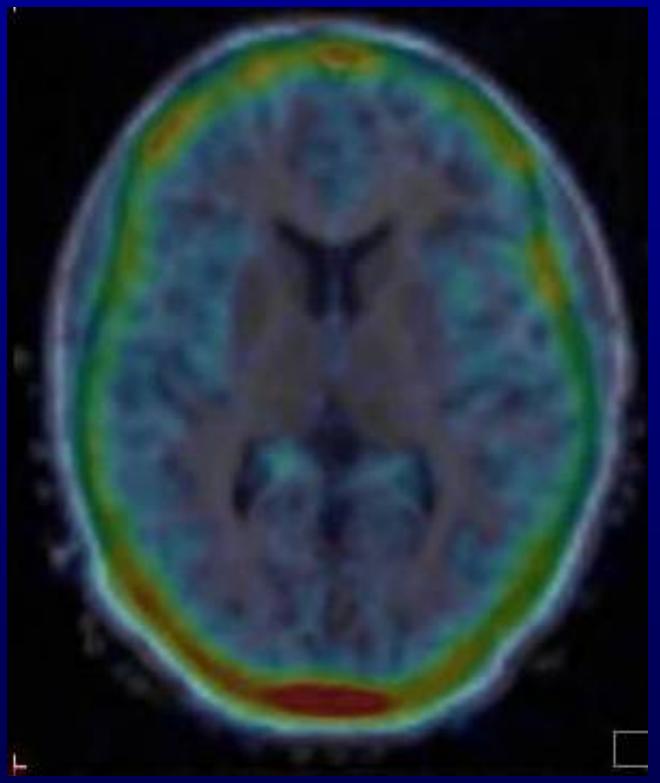
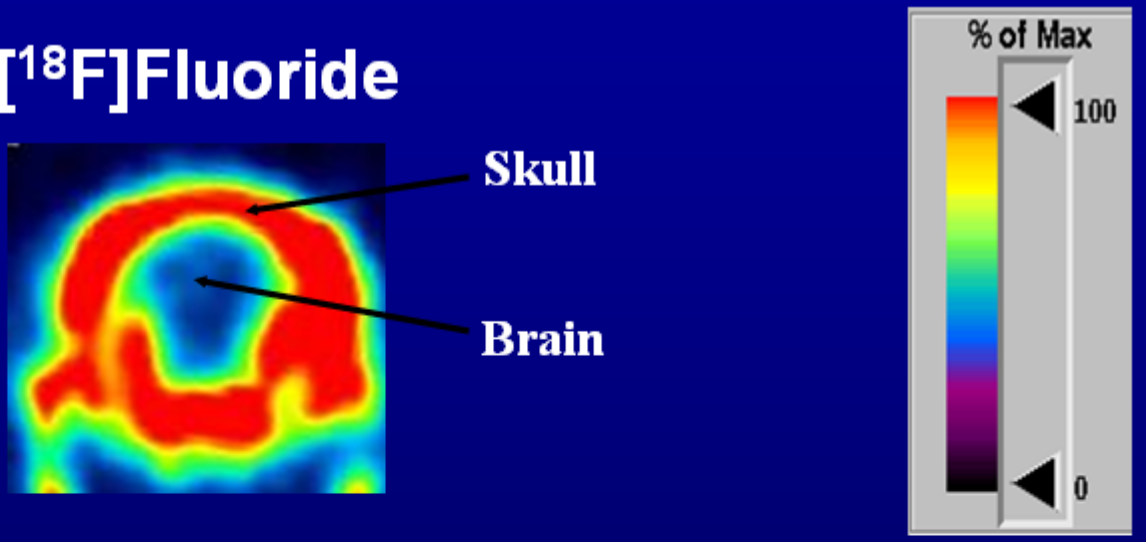
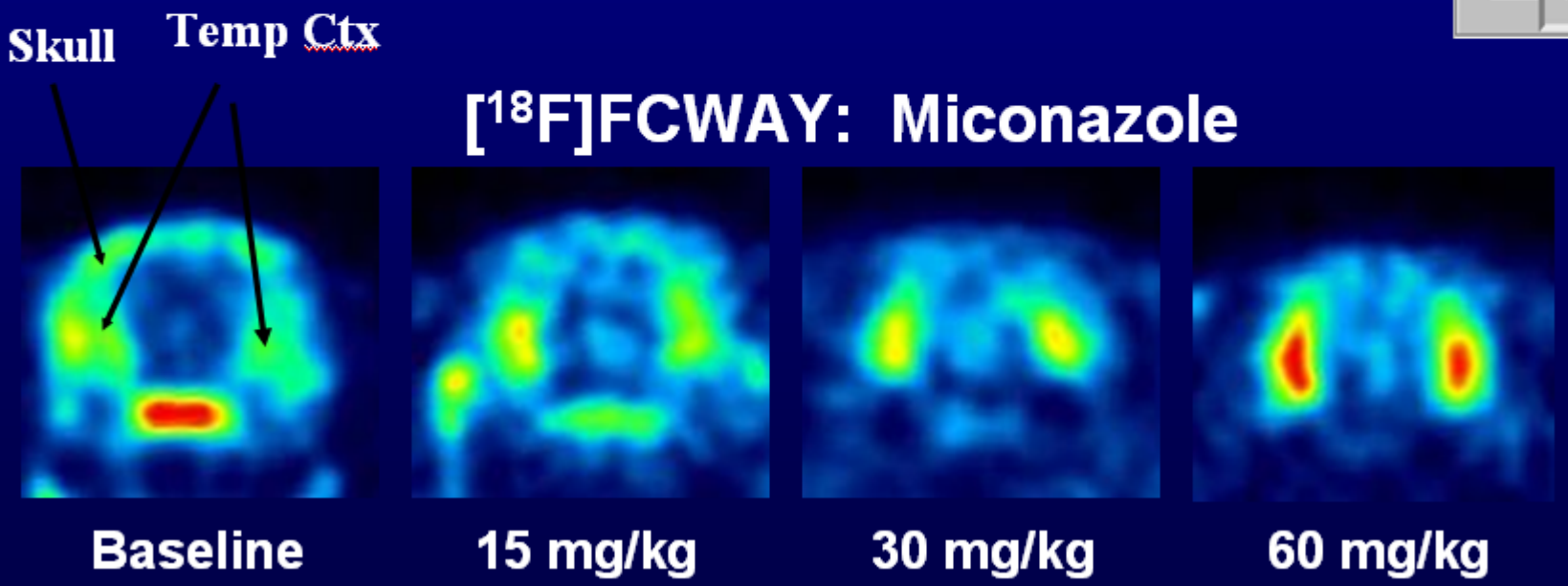
[^{18}F]FCWAY: Defluorination
Bone uptake: human skull at 2 h



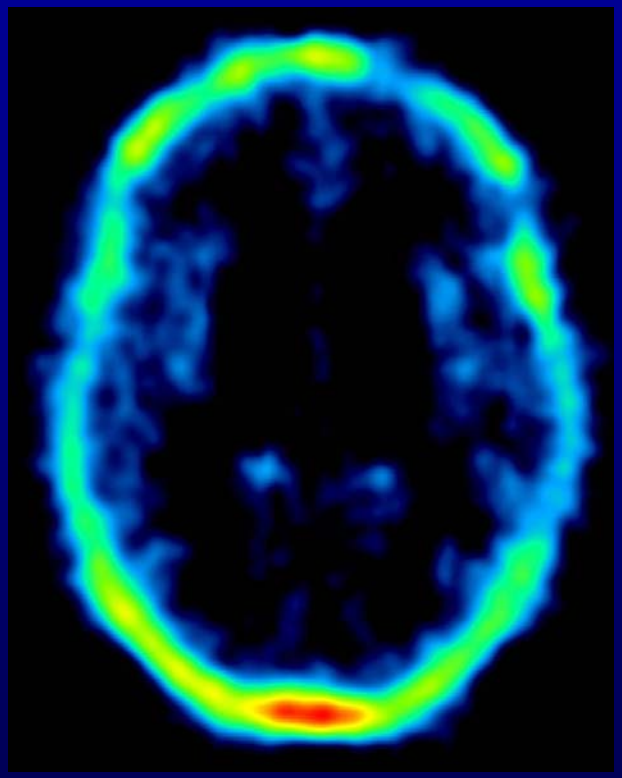


Miconazole Inhibits Defluorination & Bone Uptake

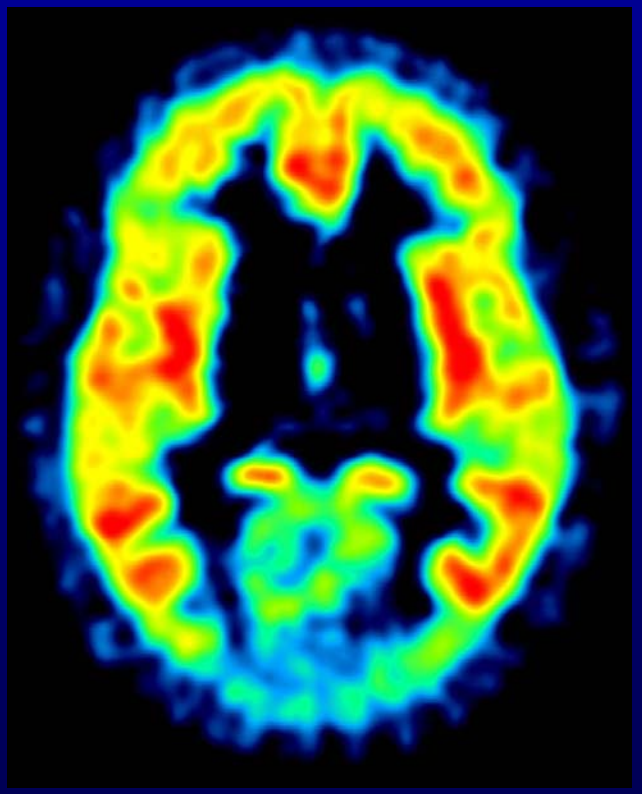




Disulfiram: Decreases Skull Activity & Increases Brain Uptake



Baseline

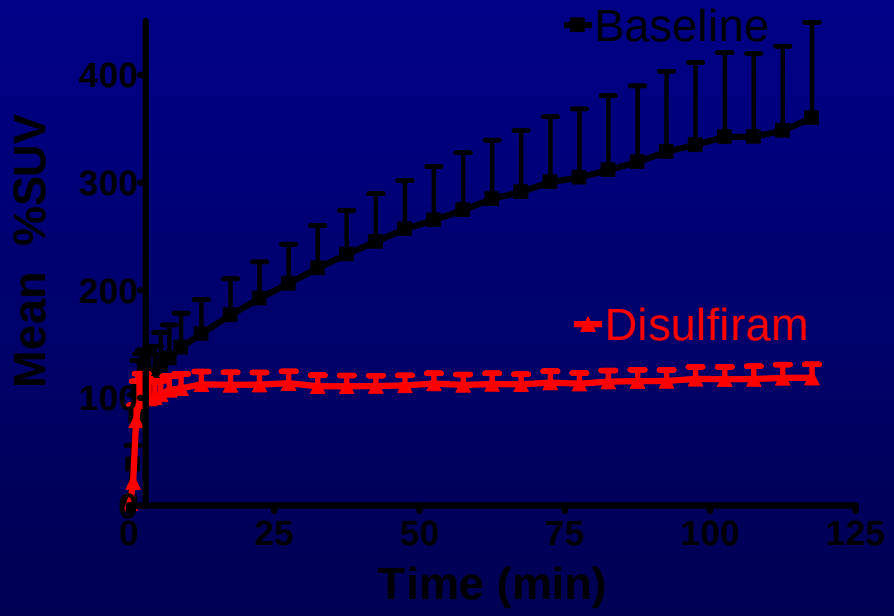


Disulfiram

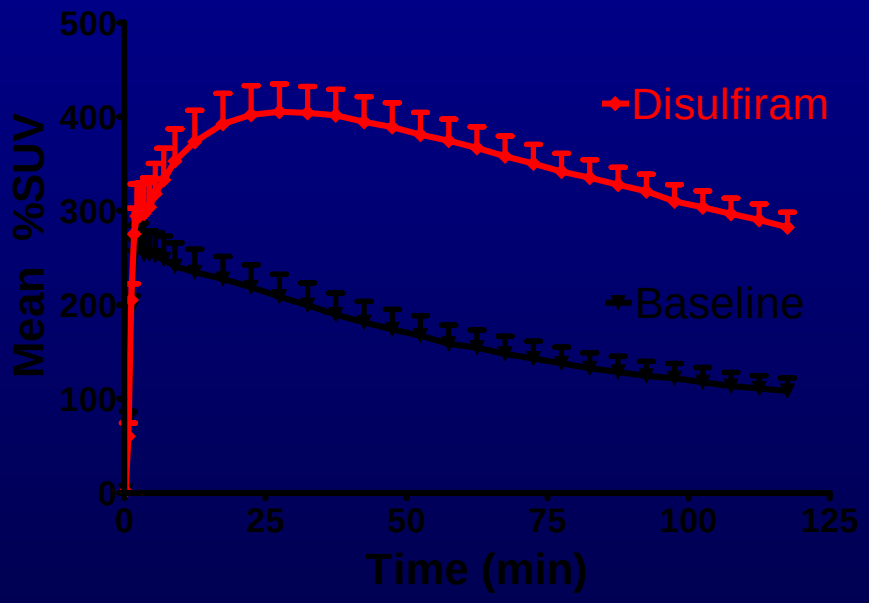
Images at 2 h in same subject. Disulfiram 500 mg PO prior night

Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of [^{18}F]FCWAY

Skull

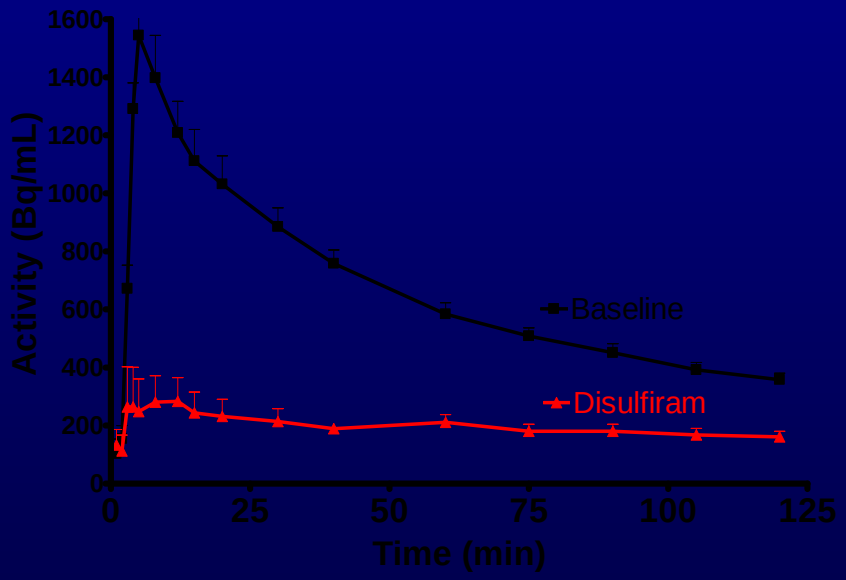


Temporal Cortex

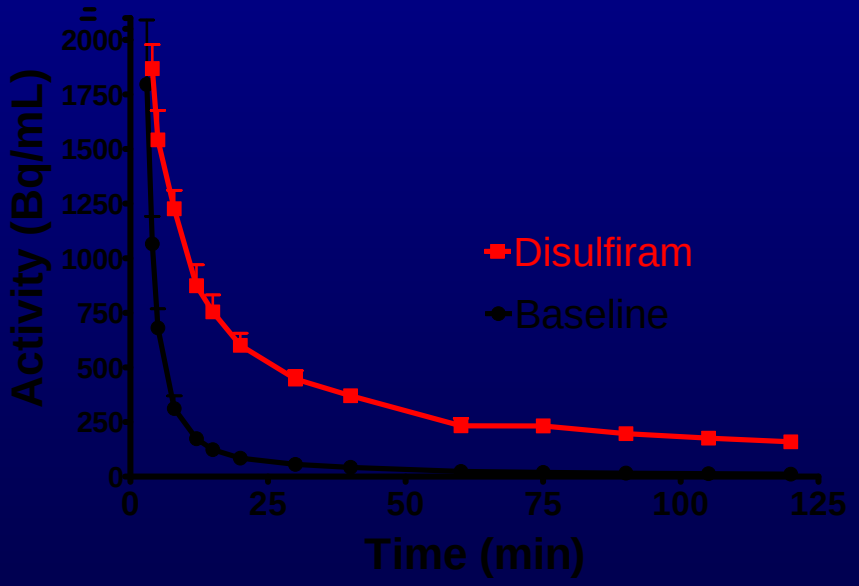


Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer [^{18}F]FCWAY

[^{18}F]fluoride



[^{18}F]FCWAY
(parent tracer)



Summary of Talk

* PET has high sensitivity and specificity
* PET used in therapeutic drug development
* Pharmacokinetic modeling: plasma concentration and tissue uptake
* Study drug distribution: “peripheral” benzodiazepine receptor
* Study drug metabolism: inhibit defluorination

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The Consortium will search for and validate new biological markers—biomarkers—to accelerate dramatically the competitive delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state. For example, cholesterol and blood pressure are perhaps the most well known biomarkers; these biomarkers are indicators of cardiovascular health.

Self-Assessment Quiz: True or False?

* Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
* PET shows the location of radioactivity in a cross section (or tomograph) of the body.
* PET can be used to quantify the density of specific proteins in the body.
* Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.